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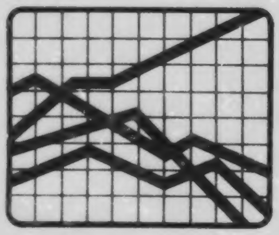
INTRAMURAL PROJECT SUMMARIES
(LISTING OF PHS 6040 FORMS)

Z01 CN 00100 CPSB	U.S.-Finland Epidemiologic Studies of Nutrition and Cancer
Z01 CN 00101 CPSB	Human Studies of Diet and Nutrition
Z01 CN 00102 CPSB	Phase I Studies of Oral Synthetic Retinoids - 4-HPR
Z01 CN 00103 CPSB	Use of Isotretinoin in Prevention of Basal Cell Carcinoma
Z01 CN 00104 CPSB	NHANES I Epidemiologic Follow-up Survey: Chemoprevention/Nutrition Aspects
Z01 CN 00105 ORB	Research in Cancer Screening Methodology and Modeling
Z01 CN 00106 ORB	Studies in Cancer Screening
Z01 CN 00107 ORB	Design and Analysis of Pharmacokinetic Studies of Selenium
Z01 CN 00108 ORB	Development of Cancer Control Epidemiology and Tracking
Z01 CN 00109 ORB	Data Management and Design of Clinical Trials for Cancer Prevention and Control
Z01 CN 00110 ORB	Methodologic Studies of Dietary Assessment
Z01 CN 00111 ORB	Consumption of Foods and Supplements Potentially Related to Cancer
Z01 CN 00112 CPSB	Nutrition Intervention Study in Esophageal Cancer in Linxian, China
Z01 CN 00113 BB	Cancer in Oriental Populations
Z01 CN 00114 BB	Morbidity Among Long-Term Survivors of Childhood Cancer and Their Offspring
Z01 CN 00115 BB	Descriptive Cancer Epidemiology
Z01 CN 00116 BB	Statistical Methodology Research
Z01 CN 00117 BB	Studies of Cancer Patient Survival
Z01 CN 00118 BB	Surveillance, Epidemiology, and End Results (SEER) Program
Z01 CN 00119 BB	Consultation on Clinical Trials and Other Studies

Director's Report



The National Cancer Institute is expanding and accelerating an aggressive research and resources development program that reflects the Institute's mission and commitment to reduce cancer morbidity and mortality. A specific goal has been set to reduce cancer mortality by 50 percent by the year 2000.

Within the NCI, the Division of Cancer Prevention and Control (DCPC) is charged with the responsibility of directing cancer control activities. A reorganization of the Division has been accomplished (with a concurrent name change from the Division of Resources, Centers, and Community Activities), resulting in a more coordinated approach to cancer control. The Division emphasizes the continuum between research, technology transfer, and cancer control surveillance activities, with the DPCP research program aimed toward achieving measurable reductions in cancer incidence, mortality and morbidity, and increased cancer survival rates.

This report outlines the Division's programs and accomplishments in FY 84 and its plans for the future. This first chapter is an overview of the Division's programs organized according to cancer control activity, while the succeeding chapters discuss each program area in more detail.

CANCER: THE MAGNITUDE OF THE PROBLEM

Before turning to the Division's programs, it is helpful to take a brief overview of the impact of cancer. Statistics can reflect only a portion of this enormous health problem, yet many of these statistics show that the prospects of surviving and preventing cancer continue to improve.

Cancer remains the second leading cause of death in the United States (Table 1). Recent estimates from the National Center for Health Statistics for the year 1980 indicate that neoplasms account for an average of 17.1 years of life lost per death as compared with 12.6 years lost from heart disease and stroke combined. It is estimated that during 1984 approximately 870,000 new cases of cancer will occur, and 450,000 Americans will die of this disease. Although the toll is large, progress is being made, and major reductions in cancer mortality are believed possible by the end of the century.

TABLE 1

NUMBERS OF DEATHS FOR THE 10 LEADING CAUSES OF DEATH*
UNITED STATES, 1980 AND 1982

		1980	1982
1.	Diseases of the heart	763,060	759,050
2.	Malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues	414,320	435,550
3.	Cerebrovascular diseases	170,420	159,630
4.	Accidents and adverse effects	106,550	96,680
	Motor vehicle accidents	54,200	46,630
	All other accidents and adverse effects	52,350	49,050
5.	Chronic obstructive pulmonary diseases and allied conditions	55,810	59,980
6.	Pneumonia and influenza	52,720	50,460
7.	Diabetes mellitus	34,230	33,220
8.	Suicide	28,100	27,860
9.	Chronic liver disease and cirrhosis	29,520	27,250
10.	Atherosclerosis	28,750	26,550

* Based on a 10 percent sample of deaths.

Source: National Center for Health Statistics.

Survival statistics continue to show progress for a number of cancer sites. In Figure 1, progress can be seen in Hodgkin's disease, testicular cancer, prostate cancer, and melanoma. NCI estimates that five year relative survival is now over 50 percent. However, five year relative survival for black Americans for all sites combined is less than 40 percent. Cancer mortality rates (Figures 2a and 2b) reflect three major trends: sites for which mortality has decreased sharply over the past half century (e.g., stomach), sites for which increases or decreases in mortality rate have been more modest, and for lung cancer, a trend that has been sharply up over the last 50 years but in males under 55 now shows signs of decreasing. If the trend in women continues unabated, however, the lung cancer mortality rate will double between 1980 and 1990.

NCI believes that major reductions in the cancer toll are possible through changes in diet, through a major reduction in smoking behavior in the United States, and through a concerted effort to improve and bring the state-of-the-art in cancer treatment and early detection to every cancer patient in the United States. The process by which NCI is formulating a set of cancer control objectives to guide its research and application activities is outlined at the end of this chapter.

FY 84 BUDGET

The total Division budget during FY 84 was $227,204,000. Of this total, $63,155,000 (28%) was devoted to cancer control activities. Each program area has a portion of its activities related to cancer control (Figure 3). Table 2 outlines the estimated budget allocation for FY 84 by funding mechanism and several of the major programs.

ORGANIZATION

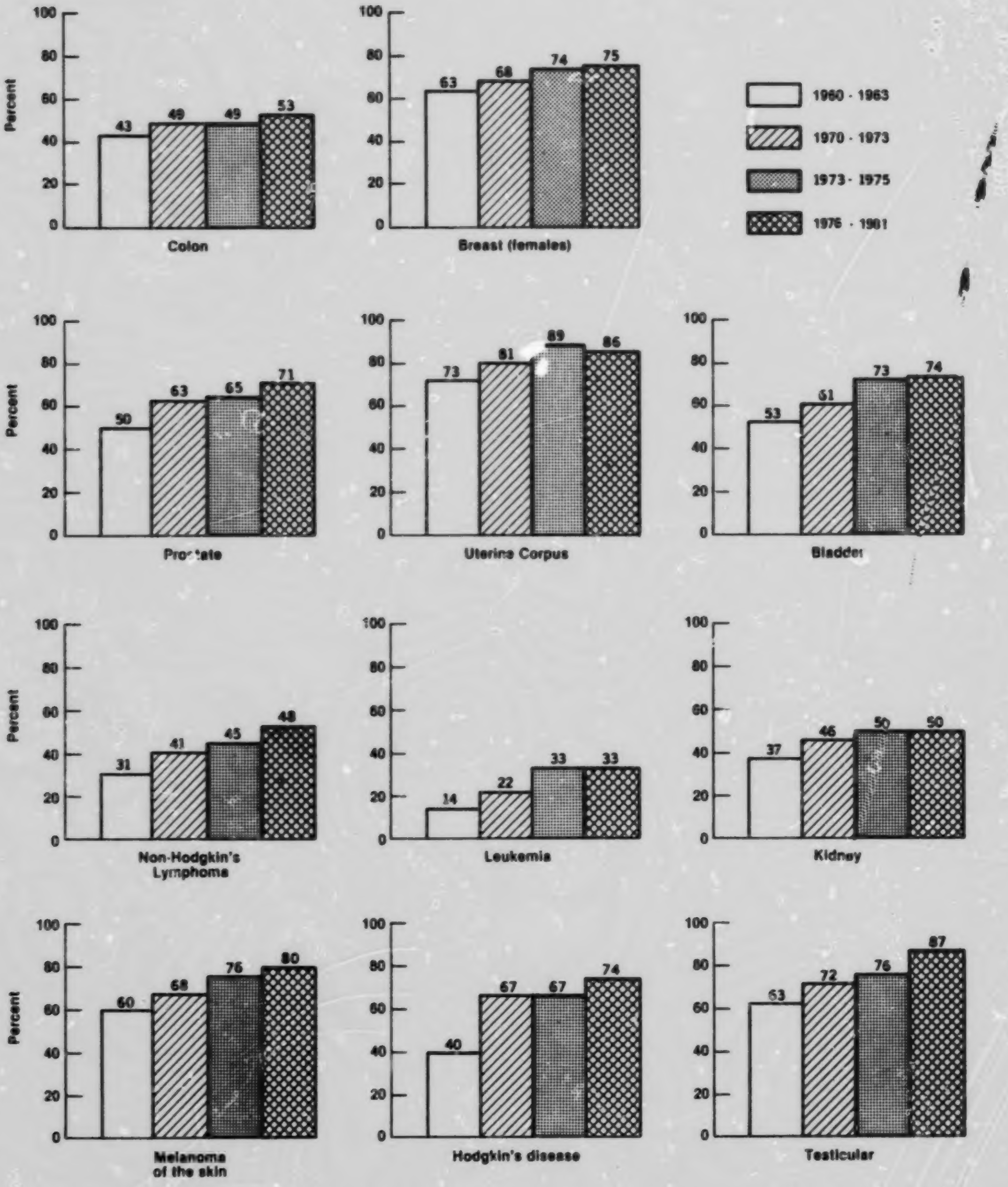
Figure 4 outlines the DCPC organization. The Division consists of three major programs, each led by an Associate Director or Special Assistant. The Office of the Division Director provides overall coordination and direction and analytic program support. Each program is described briefly below and more fully in separate chapters of this report.

The Prevention Program is charged with planning and supporting both intramural and extramural research in chemoprevention, diet and cancer, occupation and cancer, and cancer detection. In addition, this organizational unit serves as the focal point for coordinating diet, nutrition and cancer activities across the NCI divisions.

The Centers and Community Oncology Program supports shared research resources in cancer centers and applied research resources in the delivery of treatment, continuing care, and rehabilitation of patients with cancer. Within the Division of Cancer Prevention and Control, the CCO Program provides the framework for the integration of cancer centers and community activities.

FIGURE 1

FIVE-YEAR RELATIVE SURVIVAL RATES[1] FOR SELECTED SITES FOR WHITE CANCER PATIENTS



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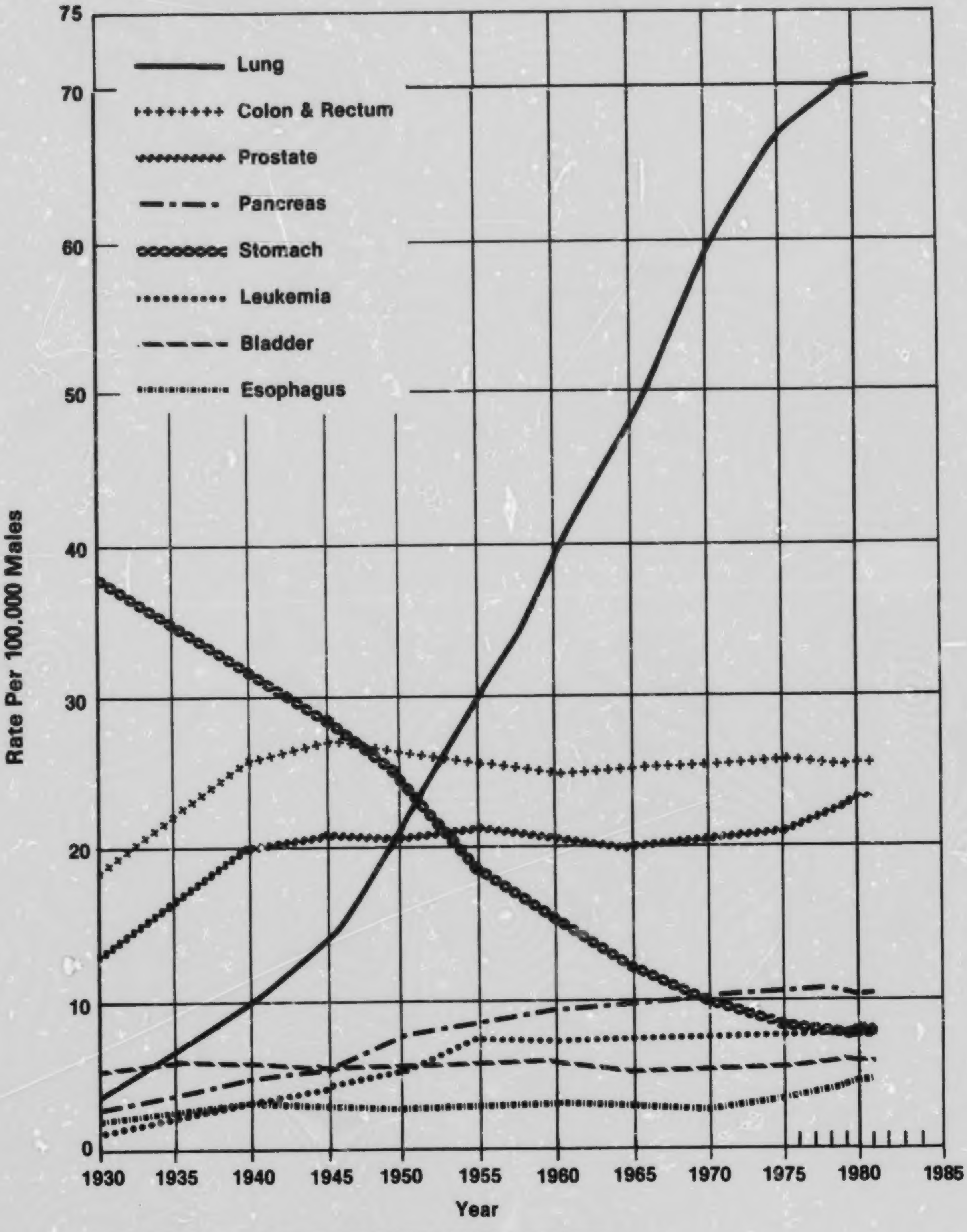
[1] Five year relative survival rate is the probability of escaping death due to cancer for five years following diagnosis. Rates for 1960–63 and 1970–73 are based on data from hospital registries and one population-based registry, those for 1973–75 and 1976–81 are from the SEER program. Rates are based on the follow-up of patients through 1982. While the data are not strictly comparable, they are indicative of change.

FIGURE 2A

AGE-ADJUSTED CANCER DEATH RATES* FOR SELECTED SITES MALES, UNITED STATES, 1930-1981



Sources of Data: U.S. National Center for Health Statistics and U.S. Bureau of the Census.
*Adjusted to the age distribution of the 1970 U.S.. Census Population

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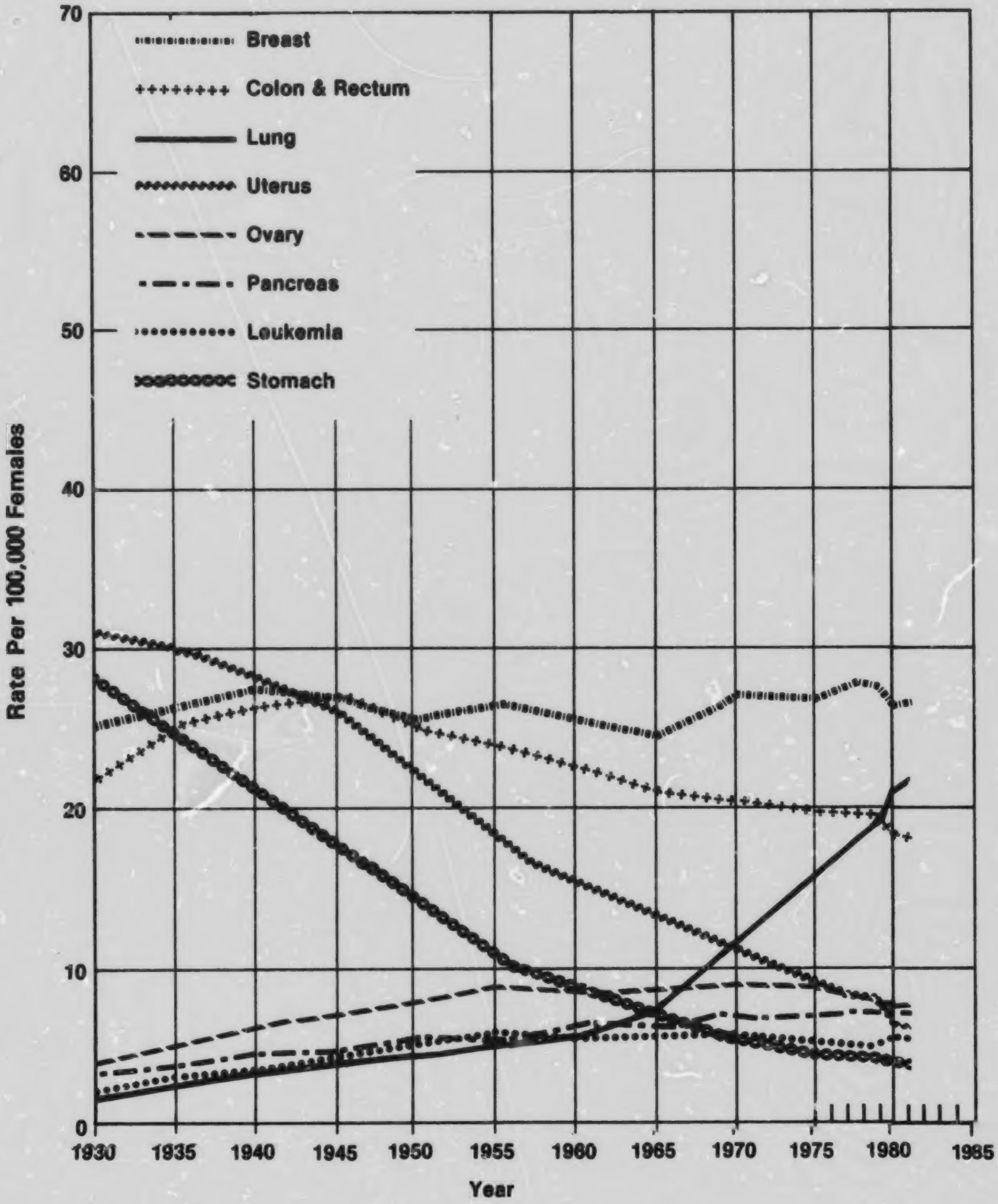
FIGURE 2B

AGE-ADJUSTED CANCER DEATH RATES* FOR SELECTED SITES FEMALES, UNITED STATES, 1930-1981

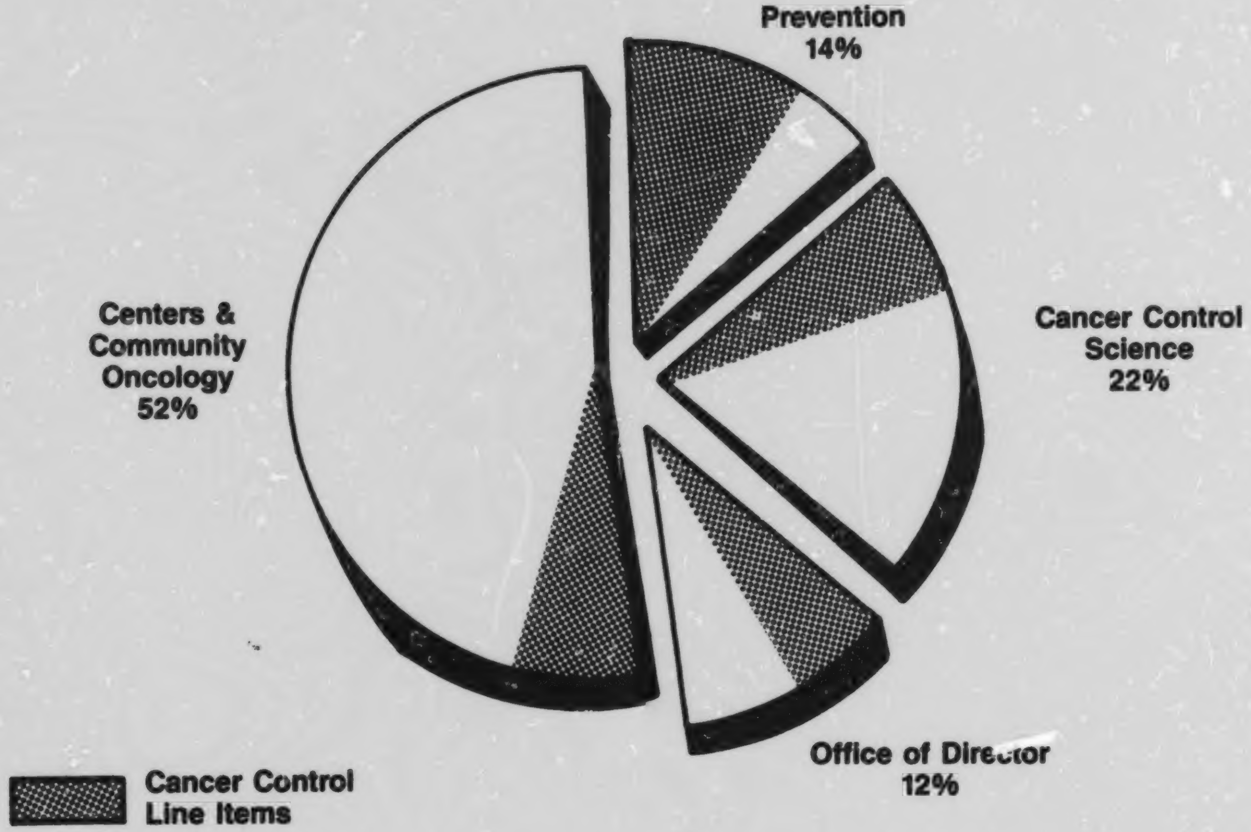


Sources of Data: U.S. National Center for Health Statistics and U.S. Bureau of the Census.
*Adjusted to the age distribution of the 1970 U.S.. Census Population

FIGURE 3

DCPC

FY 1984 BUDGET ALLOCATION*
$227,204,000



*Estimate

TABLE 2

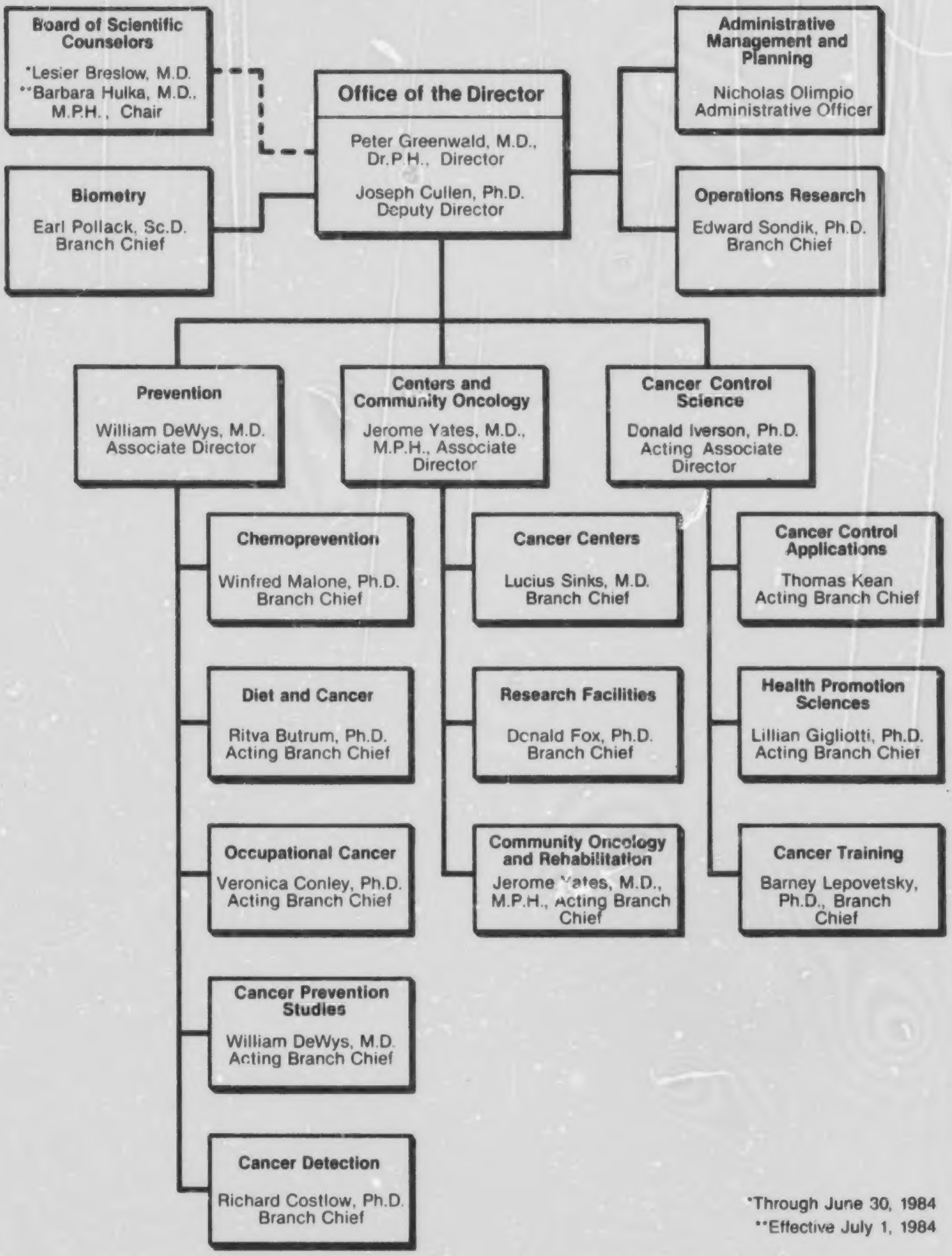
DCPC FY 1984 BUDGET
(in thousands)

CANCER CONTROL	FY 1984*
Contracts	$ 20,781
Grants	12,457
RFA	23,417
Direct Operations & Program Management	6,500
Sub-Total Cancer Control	$ 63,155
OTHER RESEARCH AND RESOURCES	
Traditional Grants	$ 21,975
Program Projects	3,912
Research Contracts	15,547
RFA	3,500
Organ Systems	750
Cancer Centers	79,000
Construction	1,000
Clinical Education	4,459
Research Career Awards	4,709
Preventive Oncology	735
National Research Service Awards	23,861
Direct Operations & Program Management	4,601
Sub-Total Other DCPC Research & Resources	$164,049
Total	$227,204

* Estimate

FIGURE 4

Division of Cancer Prevention and Control Organization Chart


Board of Scientific Counselors
*Lester Breslow, M.D.
**Barbara Hulka, M.D., M.P.H., Chair
Office of the Director
Peter Greenwald, M.D., Dr.P.H., Director
Joseph Cullen, Ph.D. Deputy Director
Administrative Management and Planning
Nicholas Olimpio Administrative Officer
Biometry
Earl Pollack, Sc.D. Branch Chief
Operations Research
Edward Sondik, Ph.D. Branch Chief
Prevention
William DeWys, M.D. Associate Director
Centers and Community Oncology
Jerome Yates, M.D., M.P.H., Associate Director
Cancer Control Science
Donald Iverson, Ph.D. Acting Associate Director
Chemoprevention
Winfred Malone, Ph.D. Branch Chief
Diet and Cancer
Ritva Butrum, Ph.D. Acting Branch Chief
Occupational Cancer
Veronica Conley, Ph.D. Acting Branch Chief
Cancer Prevention Studies
William DeWys, M.D. Acting Branch Chief
Cancer Detection
Richard Costlow, Ph.D. Branch Chief
Cancer Centers
Lucius Sinks, M.D. Branch Chief
Research Facilities
Donald Fox, Ph.D. Branch Chief
Community Oncology and Rehabilitation
Jerome Yates, M.D., M.P.H., Acting Branch Chief
Cancer Control Applications
Thomas Kean Acting Branch Chief
Health Promotion Sciences
Lillian Gigliotti, Ph.D. Acting Branch Chief
Cancer Training
Barney Lepovetsky, Ph.D., Branch Chief

*Through June 30, 1984
**Effective July 1, 1984

The CCO Program also has the responsibility of stimulating, developing, applying, and disseminating knowledge and technology related to cancer patient management.

The Cancer Control Science Program supports an integrated approach to cancer control research and applications. Program efforts are directed toward establishing cancer control as a scientific program where research on intervention strategies and their impact on populations is given primary attention.

The Office of the Director is responsible for the coordination and direction of the Division programs. It includes three branches; the Biometry Branch (BB), the Operations Research Branch (ORB), and the Administrative Management and Planning Branch (AMPB). The Biometry Branch includes the Surveillance, Epidemiology and End Results (SEER) program as well as research using SEER and other epidemiological databases, research in biostatistical methodology, and clinical trials research. The Operations Research Branch supports the Division in operations research, epidemiology, program evaluation, and computer technology. The Administrative Management and Planning Branch assists in the management of the Division budget and administrative matters. The Office of the Director is also responsible for coordinating the NCI-wide Smoking, Tobacco and Cancer Program (STCP). The activities during this fiscal year of all three branches and two coordinative bodies, the Smoking, Tobacco and Cancer Program and the Diet, Nutrition and Cancer Program, are discussed at the conclusion of this chapter.

The Division has continued to increase in size over the past year. Members of the staff are listed in the report for the specific program or branch to which they are assigned. Publications of the staff in FY 84 are cited in Appendix A.

THE DIVISION RESEARCH AND RESOURCES PROGRAMS

Cancer Control Research Framework

As an initial step in clarifying its future directions in cancer control, the NCI and its advisory boards arrived at a consensus definition for cancer control:

> Cancer control is the reduction of cancer incidence, morbidity, and mortality through an orderly sequence from research on interventions and their impact in defined populations to the broad, systematic application of the research results.

The definition captures the essential premises of the new and developing Cancer Control Program. The goal of cancer control is expressed in terms of the reduction of cancer incidence, morbidity, and mortality rates. The aim is to reduce these rates in the whole population. "Through an orderly sequence" means use of the scientific method in a progression from basic or clinical investigations to broad application in target populations. "Interventions" is a key word; cancer control, by this definition, must involve an intervention. This means that an epidemiologic study that examines an etiologic factor but does not involve interceding for the benefit of a specific patient or the general public would not fall under Cancer Control research. The definition would include, however, the application of a preventive strategy, a screening technique, a medical treatment, or a rehabilitation technique in an effort to determine its effectiveness if adopted in the community. The statement, "their impact in defined populations," is included because research on cause-and-effect relationships does not necessarily indicate how to achieve an effective, widescale impact. Research is needed on how best to achieve changes in large populations--that is, defined population research--and about the demographic characteristics of these defined study populations as a basis for generalizing from the research results.

Phases of Cancer Control Research

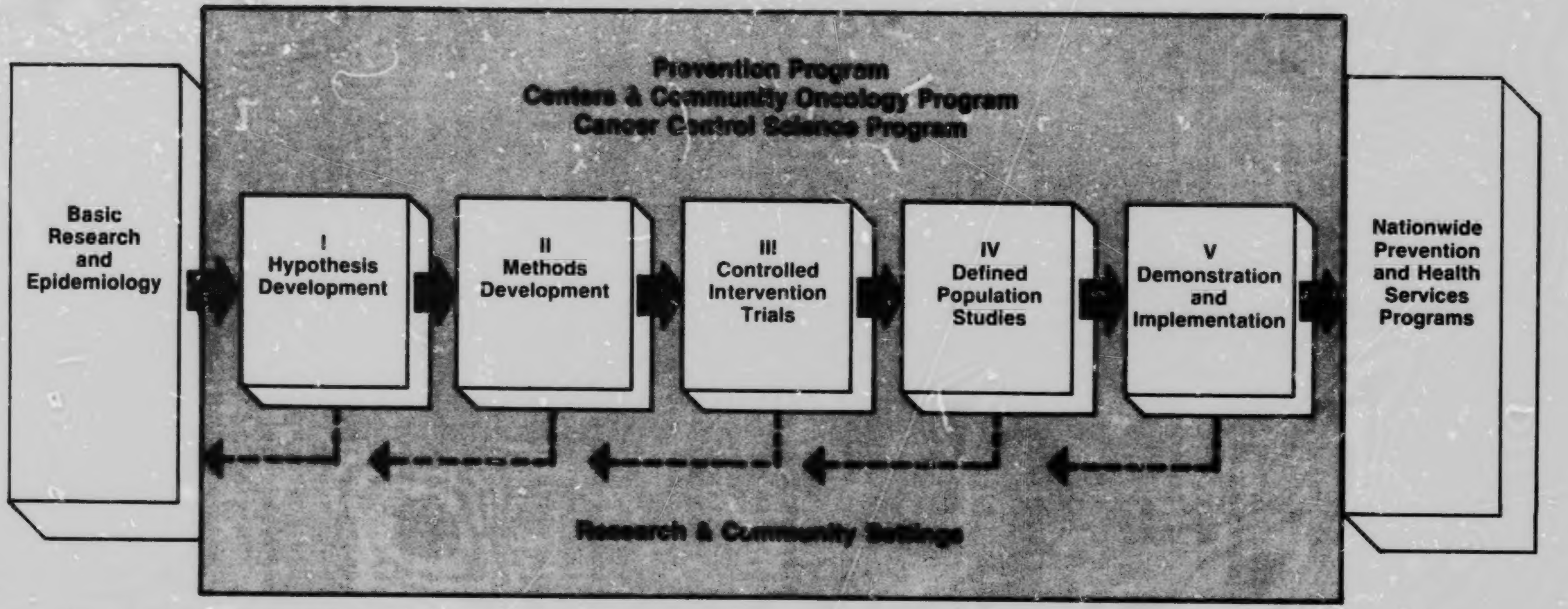
To give cancer control its required objectivity and to help research proceed most effectively, the NCI has developed a strategic decision-making model. All cancer control research is classified according to an orderly sequence of five stepwise phases of an overall research process (Figure 5). The classification applies to all cancer control research--prevention, treatment, and technology transfer: (I) hypothesis development, (II) methods development, (III) controlled intervention trials, (IV) defined population studies, and (V) demonstration and implementation studies. At the end of each phase there is a "decision point" at which criteria are reviewed to determine if research results at that point are adequate and sufficiently promising to warrant proceeding to the next phase. The NCI believes that its research efforts should give priority to cancers causing the greatest morbidity and mortality, to cancers for which substantial risk has been associated with common exposures, and to cancers for which effective actions are available.

Phase I, Hypothesis Development, is the identification and assessment of research leads based on a synthesis of available scientific evidence from basic laboratory, epidemiologic, and clinical studies. This phase of the research process results in hypotheses for cancer control strategies to be tested for efficacy in reducing incidence, morbidity, or mortality through the next four phases.

Methodological research is the focus of Phase II, Methods Development. Research in this phase characterizes the factors and outcomes which must be monitored in subsequent intervention studies to ensure that accurate and valid procedures are available before the actual study is begun. Because the spectrum of cancer control intervention is so broad, Phase II includes a wide array of possible research, including pilot tests to investigate the feasibility or acceptability of using a proposed intervention in a specific population subgroup; population compliance studies; development, pilot testing, and validation of data collection forms; testing of translations of materials from other languages; and tests of the applicability of methods used with other diseases or disciplines. As part of the Methods Development phase, interventions must be assessed in terms of their possible effectiveness and cost, as well as their risks to the subjects. When particular methods have been tested and proven in Phase II, they may be incorporated into studies in subsequent phases. Issues

FIGURE 5

Cancer Control Phases


Prevention Program
Centers & Community Oncology Program
Cancer Control Science Program
Basic Research and Epidemiology
I Hypothesis Development
II Methods Development
III Controlled Intervention Trials
IV Defined Population Studies
V Demonstration and Implementation
Nationwide Prevention and Health Services Programs
Research & Community Settings

of particular concern might include, for example, the assessment of whether long-term dietary habits can be changed and monitored accurately. In summary, this development phase lays the methodologic foundation for drawing valid inferences in the subsequent intervention stages. Validation of research methods is critical for implementing quantitative studies in Phases III and IV.

The aim of the controlled studies in Phase III, Controlled Intervention Trials, is to test the hypotheses developed in Phase I, using the methods validated in Phase II. The Phase III studies test the efficacy of an intervention in a group of individuals. In a clinical trial, the group is generally more homogeneous than the actual target population and may be chosen in a way that facilitates research management rather than as a representative sample of society. In a controlled intervention trial, the study group is compared with a control group to whom no intervention is applied; or, different interventions are compared to one another and/or to a control group.

If an intervention successfully passes Phase III, it may, depending on issues of potential impact and budget constraints, move to Phase IV, Defined Population Studies. The purpose of Phase IV studies is to quantify the impact of an efficacious intervention by applying it in a carefully controlled study of a defined population (that is, a population representative of a particular societal group). A Phase IV study is conducted in a large, distinct, and well-characterized population chosen in such a way that the study subjects are representative of, and therefore the results can be extrapolated to, the ultimate target population. The defined population may be characterized in terms of demographics, such as occupation, education, socioeconomic status; vital statistics, such as incidence, morbidity, and mortality; personal or lifestyle factors, such as diet and smoking; genetic and biological characteristics; or other factors associated with disease. Often the population will include all persons who have certain demographic characteristics and live within a specified geographic area. These characteristics allow for calculating risk factor rates (for example, smoking); incidence, morbidity, and/or mortality rates; and the changes that are estimated to result from the intervention. Phase IV studies further validate the methods developed in Phase II and the efficacy determined in Phase III, and they resolve new issues about the extrapolation of interventions to the larger population represented. At times, it may be efficient to merge Phase III and IV studies.

The Demonstration and Implementation studies in Phase V introduce the proven intervention (from Phase IV) to a community at large and measure the public health impact. To ensure that the intervention is applied uniformly with the validated methods, a system of evaluation and quality control procedures must be in place. These studies may be part of other public health program efforts, but evaluation and quality control procedures are still required.

Phase V programs are conducted only after careful research studies in each of the preceding phases provide results that justify demonstration and implementation. Therefore, at the completion of Phase V, a proven intervention with the demonstrated public health benefit of reducing cancer incidence, morbidity, or mortality would have been introduced in a population with known characteristics, and a process for monitoring the impact of the program would be in place.

Division Programs

From a cancer control perspective, the Division's interrelated programs can be grouped into five activity areas (Figure 6). First are the Prevention Program components that are directed toward reducing cancer incidence: Chemoprevention, diet and nutrition, smoking and tobacco, and occupational cancer. Second are components aimed at research to reduce morbidity and increase survival--cancer care and management oriented activities: Screening and detection, and community oncology which includes rehabilitation and continuing care. These prevention and cancer care research components are supported by the Cancer Control Surveillance and the Resource Development activities. Lastly, to translate into practical applications the knowledge learned from research in the prevention and cancer care components, the Cancer Control Science component conducts research in technology transfer and health promotion so that the public will benefit either directly or through the health system.

The following sections summarize the research in these activity areas. More detail can be found in the Associate Director's Reports.

CANCER PREVENTION

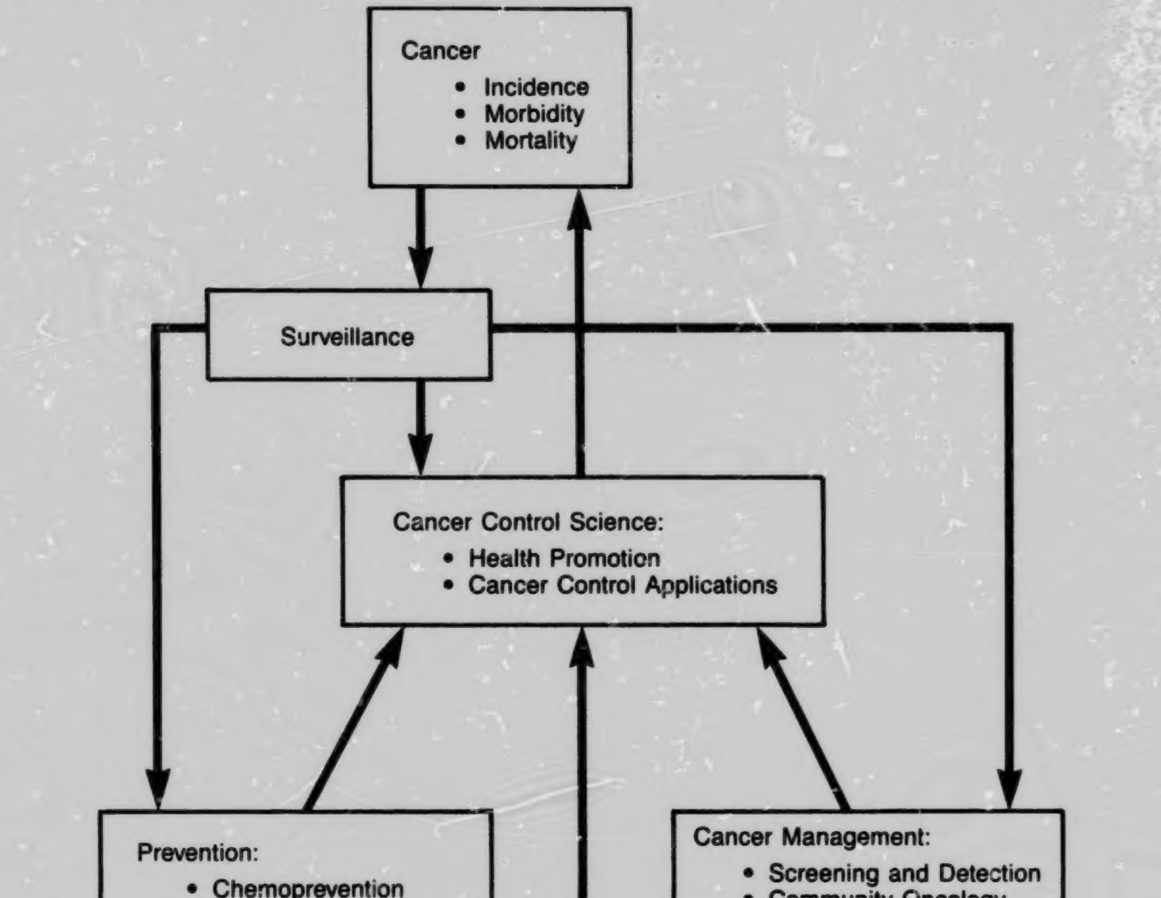
Cancer prevention research seeks to advance knowledge on ways to reduce the risk for cancer. The overall goal is to reduce cancer incidence or progression through applied research in the areas of chemoprevention, diet and nutrition, risk reduction in occupational settings and through activities related to smoking and tobacco.

Chemoprevention

Chemoprevention research has developed rapidly during the past few years. Chemoprevention is the study of the toxicity, metabolism, and mechanism of action of those micronutrients or synthetic chemicals that could be added to dietary intake to lower cancer risk. Epidemiologic and laboratory studies provide strong evidence that various natural and synthetic micronutrients may play a role in reducing the incidence of cancer in humans or in halting or reversing cancer progression in animals. Epidemiologic studies indicate that persons eating diets high in particular micronutrients have a lower incidence of certain cancers such as lung, breast, colon, and uterine. The purpose of chemoprevention research is to determine whether these natural or synthetic agents can lower cancer incidence. Should research in the chemoprevention and diet and nutrition areas prove successful, as much as 35 percent of all cancer may be preventable. Potential chemopreventive agents include several naturally occurring substances found in many foods, such as vitamin A and its precursor, beta-carotene, vitamins C and E, and the trace mineral selenium. In addition, other agents, such as phenolic antioxidants, protease inhibitors, prostaglandin synthesis inhibitors, indoles, and uric acid, are under laboratory study as potential chemopreventive agents.

FIGURE 6

DIVISION OF CANCER PREVENTION AND CONTROL: PROGRAM RELATIONSHIPS


Cancer
• Incidence
• Morbidity
• Mortality
Surveillance
Cancer Control Science:
• Health Promotion
• Cancer Control Applications
Prevention:
• Chemoprevention
• Diet and Nutrition
• Smoking and Tobacco
• Occupational Cancer
Cancer Management:
• Screening and Detection
• Community Oncology
• Rehabilitation and Continuing Care
• Organ Systems
Resources Development:
• Training
• Centers
• Construction
Other NCI Research
Basic and Clinical Research

Research of diet and cancer differs from the chemoprevention research in that the former focuses on the role of specific foods or food groups in the prevention of cancer, whereas chemoprevention focuses on the use of isolated nutrients or analogs. Diet interventions take the form of modifications of dietary behavior; in contrast, chemoprevention interventions provide for the use of precise doses of chemically defined dietary supplements.

Specific objectives of chemoprevention research include:

- Identifying and characterizing agents with proven activity in preventing carcinogenesis in animals,
- Identifying agents based on epidemiologic studies,
- Testing for efficacy and toxicity to select the most promising agents,
- Conducting Phase III human trials of potential chemoprevention agents,
- Applying research results to the general population.

A detailed plan has been developed to guide the many facets of the laboratory and human chemoprevention research which must be conducted simultaneously to achieve these objectives. Separate, sequential stages or flows of epidemiologic and laboratory research lead to a sequence of human intervention studies. The plan identifies key decision points at which results are reviewed to determine whether evidence warrants that a given intervention should proceed to the next research phase. Such plans ensure that resources are used as effectively as possible toward maximum improvement in disease prevention.

The growing body of basic and epidemiologic evidence on the inhibition of cancer suggests that chemoprevention merits aggressive research, including human intervention trials. Such trials also are necessary to evaluate toxicity and risk/benefit relationships for these agents. Clinical trials and defined populations studies will provide information basic to determining the feasibility of applying given interventions to the population at large.

Human intervention studies underway involve the use of micronutrients in defined population groups. These studies are focusing on cancer of the lung, colon, skin, cervix, and other sites. The risk groups under study include women with cervical dysplasia, heavy smokers, asbestos-exposed workers, and patients with colonic polyps, polyposis coli. For example, a study on the effect of beta-carotene in preventing lung cancer among heavy smokers has been undertaken. Heavy smokers have a risk for lung cancer that is more than 10 times that of nonsmokers. Epidemiologic studies of diet suggest that smokers who eat a diet high in beta-carotene have a lower risk of lung cancer than smokers whose diet is low in beta-carotene.

Another area of research activity is the prevention of second cancers. Patients who have been successfully treated for cancers of certain sites have an increased risk of subsequently developing another cancer of that same site.

An example is cancer of the urinary bladder. Animal studies show that the incidence of bladder cancer can be reduced by increased dietary vitamin A or synthetic modifications of vitamin A (called retinoids). Preliminary results from two human clinical trials indicate that a synthetic retinoid may reduce the incidence of subsequent cancers of the bladder in persons previously treated for bladder cancer. Further research is planned.

Other chemoprevention studies include a trial involving 22,000 physicians as subjects in the use of beta-carotene and aspirin for the prevention of cancer and coronary heart disease, respectively; two trials of topical retinoids for the chemoprevention of cervical cancer; and trials involving the use of various retinoids, beta-carotene, and other vitamins and fiber in patients with colonic polyps. In addition, four trials are investigating the prevention of lung cancer through supplementary retinol, beta-carotene, or vitamin B_{12}.

Major scientific opportunities exist to expand these studies to additional populations in order to further delineate the range of tumor types for which chemopreventive agents may be effective. Studies of populations at high risk for breast or bladder cancer are particularly appropriate and should be developed and implemented at this time. A critical need also exists to conduct human trials of new synthetic retinoids after these agents are evaluated in animal models.

Plans

Planned activities include grant support of investigator-initiated research and support of research structured according to the strategic plan for chemoprevention research. Investigator-initiated research will include epidemiologic studies searching for new leads about specific nutrients and specific sources, laboratory research on the mechanisms of chemoprevention, and laboratory research to identify new chemopreventive agents. Research will include *in vitro* and *in vivo* screening for new chemopreventive agents, research in animal models to delineate the anatomic sites and carcinogens which may be impacted by specific chemopreventive agents, preclinical toxicity studies of chemopreventive agents, human studies to determine the safe dose of new chemopreventive agents, and human clinical trials of chemopreventive agents focusing on new agents or on risk groups not currently under study.

Diet and Nutrition

The purpose of cancer control research in the diet and nutrition component is to reduce cancer incidence through dietary modification based on an understanding of the role of dietary components in the human health status, in particular on cancer development and progression. As the knowledge base about the role of nutritional factors in the development and progression of cancer continues to expand, the opportunity exists to develop and evaluate dietary modifications that potentially can prevent about 35 percent or more of all human cancer. Included in this area are studies to elucidate the metabolism of nutrients and their role in cancer causation and prevention; the interaction of genetic-nutrient-environmental factors in disease initiation or progression; the influence of nutritional factors on disease treatment and patient recovery;

the nutritional content of various foods; the effects on food of processing, retail practices, and other similar activities; and identification of the determinants of dietary practices and development of methods to change such practices by populations.

Epidemiologic and laboratory studies provide strong evidence that dietary factors play a significant role in the incidence of cancer in humans, as well as in the inhibition of one or more stages of carcinogenesis in animals. Epidemiologic and laboratory studies have shown a correlation between dietary fat intake and the incidence of cancer of the breast, colon, prostate, and endometrium.

Epidemiologic studies show an inverse correlation between dietary fiber and the incidence of cancer of the breast and colon. In animal models, dietary fiber reduces the incidence of colon cancer. Dietary fiber includes a range of chemical compounds that are relatively resistant to digestion in the human intestinal tract, and may be divided into two broad classes--complex polysaccharides and phenylpropane polymers. Polysaccharide fibers are fermented by colonic bacteria and lower the pH in the large intestine, which, in turn, may alter the metabolism of carcinogens in the colon. Phenylpropane polymers are more resistant to digestion or fermentation and increase stool bulk. Their effect may be through either the dilution of fecal carcinogens, or by the adsorption of carcinogens to polymers.

Epidemiologic and laboratory evidence now is converging toward a conclusion that some relatively simple dietary modifications may have a significant effect on cancer incidence and morbidity. Dietary fat intervention trials will show whether reduction in overall fat intake can reduce the incidence of breast cancer or its recurrence among women at high risk of the disease. In addition, support of a dietary fiber clinical trial will elucidate the effect of fiber as a preventive agent in persons at increased risk of colorectal cancer.

Additional research is needed to expand the base of information on the mechanism of action of different fiber components and on the distribution of these fiber components in different food groups. With this information, a dietary clinical trial could be developed with the goal of reducing the incidence of cancer of the breast, colon, prostate, and endometrium through reduction in dietary fat and an increase in those fiber components anticipated to have the greatest effect on carcinogenesis. This group of cancers constitutes more than one-third of all cancers; thus, a dietary intervention which could reduce the incidence of these cancers would have a major impact on the overall cancer incidence in this country.

Plans

Long-term clinical trials are being initiated in late 1984 to evaluate the effect of a reduced level of dietary fat (i.e., a 15 percent fat diet) on the incidence of breast cancer in a population of women who are at high risk for breast cancer. A second study will evaluate the impact of this low-fat diet on the risk of recurrence of breast cancer in women who have been treated surgically for breast cancer. In addition, another trial to evaluate the impact of dietary fiber on the progression of intestinal polyps to colonic cancer is in the early planning stage.

The adoption of a recommended diet will not be easy for most people because eating habits are deeply ingrained. Therefore, additional research is planned to better understand the information and behavioral strategies which may help people change their diets. These studies will focus on short-term changes and long-term adherence to a recommended diet. The dietary changes to be studied initially will be a reduction in dietary fat and an increase in dietary fiber. As knowledge of dietary components increases, future dietary modification studies will include foods having a specific fiber composition, as well as foods rich in specific micronutrients.

Smoking, Tobacco and Cancer Program

Fifty-four million Americans--one in every three adults--smoke cigarettes regularly. Over six million teenagers smoke on a daily basis. More than 100,000 pre-teenagers are habitual smokers. Nearly 4,000 youths begin smoking every day. At the same time, the Surgeon General has identified cigarette smoking as the major single cause of cancer mortality in the U.S.--over 130,000 Americans will die of cancer this year because of the higher overall cancer death rates for smokers than for nonsmokers. Further, lung cancer rates have increased 172 percent among men and 256 percent among women since 1953. Smokers of two or more packs of cigarettes daily have lung cancer death rates 15 to 25 times greater than nonsmokers and associations have been identified between cigarette smoking and laryngeal, oral, esophageal, bladder, kidney, pancreatic, and stomach cancers. The Surgeon General, Dr. C. Everett Koop, has stated that "Cigarette smoking is the chief, single, avoidable cause of death in our society and the most important public health issue of our time."

In the past, the NCI has contributed considerable resources to investigating smoking, other tobacco use, and cancer mortality patterns. More recently, a planning effort was initiated, bringing staff together with more than 100 extramural scientists, health administrators, and interested individuals from the private business sector to outline goals, strategies, and target populations for a broadly based intervention program designated as the NCI's Smoking, Tobacco, and Cancer Program (STCP) coordinated through the Office of the Director of the Division of Cancer Prevention and Control. The goal for the STCP is to decrease the incidence and mortality of cancer, caused by, or related to, smoking and the use of tobacco products.

The approach outlined to achieve this goal is to develop and implement an intervention research effort based on sound biomedical and behavioral research findings that will lead to a variety of health promotion and information strategies. The STCP will utilize a number of NCI units in this effort, including its epidemiologic and etiologic research resources through the Division of Cancer Etiology, and its information and dissemination resources through the Office of Cancer Communications. But the primary emphasis will be placed on carrying out controlled intervention trials, defined population studies, and, where feasible, demonstration programs through the Division of Cancer Prevention and Control.

As a result of the planning meetings described above, the following intervention strategies were selected for implementation:

- Mass media: Such approaches to the prevention and cessation of smoking and tobacco use have the potential to reach thousands of smokers at one time, offer a convenient and inexpensive means for obtaining assistance with quitting, and can contribute to fostering a social climate that is supportive of prevention and cessation behavior.

- School-based: The initiation of tobacco use is primarily an adolescent phenomenon; schools are settings in which virtually the entire population of youth can be reached. The most cost-effective way to reduce cancer mortality related to tobacco use is to prevent the initiation of the use.

- Physician/dentist change agents: These health providers are uniquely qualified in health matters, enjoying both prestige and credibility as sources of health-related information. Preliminary studies already suggest that millions of Americans could be helped to stop smoking by even modest intervention efforts from physicians and dentists.

- Self-help: Thirty-three million Americans stopped smoking since the first Surgeon General's Report on the health consequences of smoking; the vast majority of these individuals stopped without organized formal smoking cessation programs. In addition, most current smokers state that they prefer to use self-help procedures to quit.

- Worksite: The majority of American adults work and are approachable in a relatively structured setting where there is an opportunity for individual and group interaction as well as follow-up and continued maintenance.

The planning groups also identified a priority list of target populations for these intervention strategies:

- Heavy smokers: These individuals are at greatest risk for cancer.

- Minorities: There are excessively high smoking-related death rates among blacks, and an increase in smoking prevalence rates among Hispanics.

- Women: Lung cancer mortality is increasing among women and evidence shows that women who smoke are more resistant than men to cessation. Smoking prevalence among teenage girls (ages 17-18) continues to increase.

- Youth: Prevention is the most cost-effective approach and cessation of tobacco use is easier to achieve before addictive patterns are established.

- Smokeless tobacco users: The fastest growing segment of tobacco users is using tobacco products that are not smoked, but are chewed and dipped. Not only does the habit lead to oral cancer, it is also highly probable that the inevitable nicotine addiction will lead smokeless tobacco users into cigarette smoking. These products are now being used by more than 12 million Americans, with the greatest increased use among the young.

The STCP will be an important component of the Institute-wide effort to reduce cancer mortality 50 percent by the end of the century. Nearly 85 percent of lung cancer is caused by cigarette smoking; thus, efforts to reduce the percentage of smokers in the nation and to prevent nonsmokers from forming the habit hold great promise toward reducing cancer incidence and mortality.

Plans

Surveys have shown that public awareness about the dangers of tobacco use, particularly cigarette smoking, is at a new high, and that the tide of public opinion has turned against cigarette smoking. Through the initiation of a comprehensive intervention research program, combined with continued health promotion and information dissemination, the NCI can identify those strategies with the greatest effectiveness in preventing the onset of tobacco use or in promoting smoking cessation.

Future activities of the Smoking, Tobacco, and Cancer Program include implementation of the media, self-help, physician/dentist, school, black and Hispanic, heavy smoker, women, and smokeless tobacco user initiatives which already have been set in motion. Other initiatives under consideration include worksite activities, development of a smokeless generation program similar to those now active in Canada and Sweden, and a policy research program. All of these research programs will be monitored and coordinated by STCP staff and, by 1990, the most effective of these programs will be eligible for large-scale demonstrations.

Occupational Cancer

The primary objective of occupational cancer research is to reduce the incidence of cancer from all risk factors in populations that are at higher risk because of occupational status. To meet this objective and to provide continuity of occupationally related cancer projects sponsored by NCI and other agencies (such as the Occupational Safety and Health Administration (OSHA) and the National Institute of Occupational Safety and Health (NIOSH)), four research emphases are supported:

- Community-based intervention: Research and demonstrations of cancer risk education and information dissemination in occupational settings, involving community physicians, employers, and workers' unions in cooperation with local medical schools;

- Model education: The design and preparation of materials for high-risk workers;

- Evaluation: Studies to measure the impact of preventive education on behavior change in the workplace;

- Clinical-based interventions: Studies to develop appropriate medical surveillance methodologies for specific occupationally linked cancers.

The following examples illustrate the wide range of program activities and their importance to cancer control and the interrelationship of organizations necessary to accomplish the research.

Community-Based Occupational Cancer Intervention

The Workers Institute for Safety and Health (WISH) has received a grant to develop and implement community-based cancer intervention programs for 12,000 members of the Pattern Makers League of North America believed to be at high risk for developing colon/rectal cancer. The causes are not known, but the higher rate of cancer observed in three independent epidemiologic studies of pattern makers might be associated with exposure to wood dusts, solvents, adhesives, and other chemicals. The study involves education to prevent future exposures and medical surveillance to reduce cancer morbidity. Medical surveillance is financed in cooperation with the employers and is generally provided by community physicians. A similar program was established by WISH in Augusta, Georgia, (in collaboration with NIOSH) for about 1,000 workers known to have been exposed to beta-naphthylamine, and at risk for bladder cancer. A third group followed under this grant is an asbestos-exposed cohort of 1,200 workers in Port Allegany, Pennsylvania. The medical surveillance in this group is in collaboration with the Mt. Sinai School of Medicine in New York.

Educational Evaluation Studies

A number of studies are being funded to determine effective cancer control education approaches and methods to reduce or eliminate exposures to cancer hazards in occupational settings. The International Brotherhood of Painters and Allied Trades, in collaboration with Harvard University, is conducting a study of cancer control in high-risk painters exposed to solvents. The United Steelworkers of America, in cooperation with the University of Pittsburgh, is conducting a study of cancer control that reduces exposure to coke oven emissions in steel plants. The United Rubber, Cork, Linoleum and Plastic Workers of America is collaborating with the University of North Carolina at Chapel Hill in a study to alter worker behavior to reduce exposures to cancer risks in 30 rubber manufacturing plants. In addition, the International Union, United Auto Workers, is comparing the effectiveness of two educational strategies aimed at motivating workers to recognize and reduce exposure to carcinogens in automobile assembly plants. The International Chemical Workers Union, in collaboration with the University of California at Los Angeles, is conducting a nationwide field experiment (trial) to evaluate the effectiveness of an educational intervention program to reduce carcinogen exposures in chemical manufacturing plants.

Occupational Cancer Research Network

The National Cancer Institute is supporting university centers, in Cooperation with the National Institute for Occupational Safety and Health to conduct occupational cancer control hazard evaluation studies. These studies will enhance the NCI research capabilities, reduce potential duplication of effort, and increase the speed at which such research results lead to change in practice. The initiative will emphasize occupational cancer hazard evaluation to identify potential future interventions, study populations, and problems. These studies will form background for controlled clinical trials to be conducted by the National Occupational Cancer Control Clinical Research Network, which will include cooperative intervention studies to assess changes in biological end-points of specific cancer sites for which defined occupational populations are at elevated risk.

Plans

The ability to significantly reduce morbidity and mortality caused by occupational exposures by the year 2000 depends on the development of new, more effective screening and detection techniques for use with high-risk populations. The development of surveillance systems is essential to tracking and assessing the impact of future occupation-related prevention and control activities on the mortality and morbidity figures for specific occupations. To be able to measure the impact of prevention activities, the research must be undertaken in the 1980s. Planned activities will expand current efforts and will identify screening and detection and surveillance as research emphases. In addition, efforts will be initiated or intensified in the following areas:

- Biohazard control: Studies of occupational exposure controls for biohazards that may affect employees, including health care and laboratory work environments;

- Organizational interventions: Studies of the structures, approaches, impediments, and opportunities that affect research on occupational cancer control interventions, including widespread application of the findings of occupational cancer control intervention research;

- Working meetings: Planning meetings on the topics of (1) cancer control science for occupational populations and (2) interventions for occupational exposures to asbestos and aromatic amines. Plans will be developed for research cooperation with (1) state and local health departments, (2) professional organizations and societies, and (3) international organizations and agencies.

CANCER MANAGEMENT RESEARCH

The cancer management research components advance knowledge about how to decrease morbidity and increase survival through improved and early screening and detection techniques, through community oncology research directed toward provision of optimal care in the community, and rehabilitation, and through continuing care interventions.

Screening and Detection

The purpose of screening and detection research is to achieve the earliest diagnosis and, thereby, the most effective treatment strategy for cancer patients. The objectives of screening and detection research are as follows:

- To identify new research findings important to early detection of cancer;
- To further develop and ensure sensitivity, specificity, validity, and safety of measures for the early detection or diagnosis of cancer and to evaluate such programs when applied to defined populations;
- To analyze, evaluate, and refine strategies for cancer detection and diagnosis to ensure maximum benefits to the largest possible population with the least risk and cost;
- To evaluate cost/benefit or risk/benefit of early detection interventions and the means for quality control and monitoring of screening activities;
- To apply early detection interventions to the general population.

Current program emphases in support of these objectives include screening and detection studies in breast, colorectal, gynecologic, and lung cancer, as well as radiation quality assurance and risk reduction programs. All activities emphasize expeditious transfer of the research results to practice. Several program activities are described below.

Breast Cancer

The Breast Cancer Long-Term Follow-Up Study is representative of those studies being conducted in the area of breast cancer screening. The results of these and other studies will expand available knowledge on strategies for detecting and diagnosing breast cancer at an early stage. The Follow-Up Study involves 64,000 women of the more than 280,000 women who were enrolled in the Breast Cancer Detection Demonstration Program (BCDDP). The BCDDP tested the feasibility and efficacy of large-scale breast cancer screening programs. The Follow-Up Study includes women with breast cancer, women with benign breast disease, women free of breast disease, and women referred to surgical consultation, but not receiving an aspiration or biopsy. The 28 interview centers are in the fourth year of the 5-year follow-up. Overall, the project has a 97.2 percent success rate in tracing the subjects. The Breast Cancer Long-Term Follow-Up Study will allow the NCI to estimate more precisely the risk of developing breast cancer. It provides detailed information about the biology and natural history of breast disease for specific, defined groups of a screened population. This information is essential for developing cancer control strategies to reduce the morbidity and mortality caused by breast cancer.

Colorectal Cancer

The National Polyp Study is evaluating the benefits, risks, and costs of a screening program for colon cancer for patients who have had polyps removed. Seven study groups, coordinated by the Memorial SloanKettering Cancer Center, are working to answer the following cancer control questions:

- Should examinations after polypectomy be performed routinely, annually, or every 3 years?
- Should both one-year and three-year searches be done?
- Should either x-ray or endoscopy or both be perfomed as the primary follow-up examination method?
- What is the value of the fecal occult blood test in an interval examination?

These questions will be answered by a comparison of examinations by barium enema, air-contrast x-rays (pneumocolon), and colonoscopy. The role of the fecal occult blood test will also be evaluated and the overall benefits, costs, and risks of the diagnostic methods will be compared. In addition to developing recommendations about the best methods of follow-up, the study will gather data prospectively on the natural history of adenomatous polyps.

In another clinical trial on the efficacy of screening for colorectal cancer, the single intervention being studied is the addition of a hemoccult test at the time of routine screening. The objective of the study is to determine whether a hemoccult screening program can reduce the overall mortality from colorectal cancer. The study has involved 22,500 persons and is of sufficient size to answer the question of effectiveness. If it is shown that using this screening technique benefits health and lowers mortality, the study will have important applications for the general public.

Lung Cancer

Three cooperative, randomized clinical trials to evaluate the efficacy of sputum cytology and chest x-ray as screening methods to detect early lung cancer are nearly complete. While sputum cytology appeared to have promise as a screening technique, none of the studies provides evidence that mass screening by chest x-ray and sputum cytology followed by prompt, appropriate therapy reduced mortality from lung cancer. The findings of the studies are important in that, without them, health care resources might have been expended on the technology without a return in improved health.

Radiation Quality Assurance and Risk Reduction

The uses of radiation in medicine for diagnostic procedures have become more varied and useful. Radiation is used to treat cancer; more than half of all cancer patients will receive radiotherapy. The emphasis of screening and detection research has been not only on improvement in these diagnostic and therapeutic technologies but also on protection and an avoidance of unnecessary radiation.

The Regional Centers for Radiological Physics (CRP) provide quality assurance and risk reduction activities in therapy, as well as diagnostic radiology. These centers review the physics support at all facilities in the NCI-affiliated clinical programs, and serve as a resource for quality assurance, technology transfer, and education of the radiological community. The CRP coordination program, conducted by the American Association of Physicists in Medicine, ensures national uniformity in the nature and quality of activities performed by the consensus development, and evaluates the impact of the Centers for Radiological Physics on the cancer control effort. As of February 1983, the CRPs have conducted 1,020 reviews of 500 different radiation generators at 400 different facilities. These include reviews of cobalt machines, accelerators, and betatrons. The current number of radiotherapy facilities at which the CRPs carry out reviews is 267. The percentage of facilities meeting the 5 percent tumor dose delivery criteria on the first review was 78 percent; at the time of the second review there was considerable improvement, with 89 percent meeting the criteria.

Plans

The following activities are planned for screening and detection research:

- Long-term follow-up of breast cancer screenees will be continued to increase understanding of factors associated with breast cancer incidence and survival, and to utilize the cohort for appropriate prevention studies as a basis for reversing or stopping the cancer process in humans.
- Research on automated cytometric examinations may reveal early subcellular changes not discernable by conventional cytopathology. If there is a positive correlation between those changes and lung cancer, the earlier detection may reduce mortality.
- Development and testing of novel markers for early detection of cancer will be pursued. Research applications of new detection technologies may lead to recognition of cancer earlier in its natural history, more precise diagnosis, better planning for effective treatment, and reduced mortality.
- Research detection of specific and unique biochemical and/or biophysical changes (genetic or immunological markers) in cancer development will enhance early detection of cancer.
- Research on cervix cancer screening will focus on reducing cervix cancer deaths through screening, and improving quality of pap smears and cytology reading.
- A planned cancer control initiative designed to reduce mortality from malignant melanoma through application of screening and health promotion will be expanded.

AVAILABLE

- The use of monoclonal antibodies as an early detection technique for ovarian cancer or other appropriate cancer sites will be explored.

- The feasibility of new diagnostic imaging techniques (Nuclear Magnetic Resonance) for breast cancer detection will be determined and comparison made of their efficacy to mammography, including sensitivity, specificity, and cost-effectiveness.

- The feasibility of using new diagnostic imaging techniques for the early detection of lung, bladder, prostate, or colon cancers will be explored. This leads to recognition of cancer earlier in its natural history, more precise diagnosis, better planning for effective treatment, and reduced mortality.

- Effects of using specific new vaccines as cancer preventive measures, such as the human T-cell antigen, herpes, hepatitis, or AIDS vaccines, will be studied as they are developed. Surveillance and detection will be linked to these trials. From these, public health measures can be designed and implemented to lower incidence of specific cancers through primary prevention.

- If warranted by current research, a controlled clinical trial using Nuclear Magnetic Resonance as an early detection technique to reduce mortality to colorectal, lung, breast, prostate, and bladder cancer will be implemented.

- Breast and ovarian cancer screening research efforts will be expanded in coordination with health promotion activities.

Community Oncology Activities

The Community Oncology program, directed toward the provision of optimal cancer patient care in the community, includes the Community Clinical Oncology Program (CCOP), the Cooperative Group Outreach Program (CGOP), and the Community Hospital Oncology Program (CHOP). These programs are discussed in the following sections. More than 80 percent of cancer patients are treated in the community.

Community Clinical Oncology Program

Clinical trials designed to reduce morbidity and mortality from cancer are a form of cancer control. During the past decade, increasing numbers of highly trained clinical cancer specialists experienced in clinical research and protocol care have entered community private practice and are available to extend clinical trials to community patients. Evidence exists that community physicians participating in clinical research activities can effectively test new technologies and maintain the high quality research of academic centers. The Community Clinical Oncology Program is a major research initiative specifically intended to involve community physicians in clinical trials using NCI-approved research protocols.

The objectives of the CCOP are to:

- Expedite the application of advanced cancer care technology to communities;
- Bring the benefits of clinical research care to patients in communities;
- Increase participation in high-priority protocols, thus reducing the time necessary to answer critical research questions;
- Use research protocols as educational tools to help oncologists in community practice maintain state-of-the-art cancer care;
- Create a network for controlled distribution of experimental cancer agents;
- Create a resource for implementing cancer control and prevention research initiatives of the NCI.

The CCOP can be considered one of the best continuing medical education programs yet devised. Just as the universities have utilized research trials as educational tools for residents and fellows, the CCOPs will teach community oncologists by involving them as researchers. Their participation in state-of-the-art cancer care should ultimately benefit most community patients. It is expected that by involving community oncologists in clinical research, questions about the benefits of new therapies will be answered more quickly and the knowledge will be applied to other cancer patients in community settings.

Each CCOP is required to enter or refer patients into clinical trials designated as high priority by a research base currently sponsoring NCI-approved clinical research protocols. These research bases are responsible for protocol development and data collection and analysis. Each CCOP may have up to five research bases. The 62 currently funded CCOPs are affiliated with 14 Cooperative Groups and 17 Cancer Centers. Participants are encouraged to enter patients with early stage disease with common cancers and to enter or refer, if appropriate, patients with uncommon cancers.

Cooperative Group Outreach Program

The Cooperative Group Outreach Program seeks to upgrade the skills of community physicians and other health professionals in treating cancer patients and to increase the number of these patients receiving the best available care. Ultimately, the goal is to reduce cancer morbidity in the community. The objectives of the CGOP are to:

- Strengthen and enlarge the affiliated hospital programs of the Cooperative Group to increase the number of community health professionals using well-defined and monitored protocols for managing cancer patients,
- Provide support services to community physicians to maintain a high standard of patient care and data collection,

- Institute quality control of patient management by the analysis of treatment data to ensure high standards of care for patients entered on treatment protocols,

- Provide continuing education activities for community health professionals.

To date, more than 2,000 community physicians in more than 700 hospitals have participated in this program, and more than 14,000 community patients have been enrolled into group protocol studies. The program will be continued for an additional three years and evaluated as part of the Integrated Evaluation of Community Cancer Care Programs, described below.

Community Hospital Oncology Program

The Community Hospital Oncology Program is a unique community-initated effort to improve quality of cancer care delivery through maximum participation of community physicians and other health care providers in the development of state-of-the-art guidelines for patient management and monitoring of care. The principle behind the CHOP is to fund communities directly to support their search for the latest technology in cancer management. CHOP activities include:

- Developing community multidisciplinary management guidelines for medicine, nursing, and continuing care;

- Organizing the community to provide the most up-to-date care according to guidelines;

- Developing data management capabilities to monitor care;

- Developing relationships with major cancer centers for referrals when appropriate.

The program is scheduled to be completed in FY 84 and will be included in the integrated evaluation of community programs discussed below.

Evaluation of Community Cancer Care Programs

During FY 83, the NCI launched a major evaluation of its community cancer care programs. The purpose of the project, known as the Community Cancer Care Evaluation, is to conduct an integrated evaluation of the Cooperative Group Outreach Program, the Community Hospital Oncology Program, and the Community Clinical Oncology Program. The primary goal of each of these programs is the same: to establish a mechanism to facilitate the tran sfer of new patient-care technology to the community and thereby provide the highest quality cancer management to patients in the community setting. Likewise, the evaluation issue is the same across all three programs: To what extent have these programs been successful in assuring the transfer of new patient management technology, thereby providing state-of-the-art cancer care at the community level, and which elements or combinations are most effective in ensuring high-quality cancer care for all patients?

The Community Cancer Care Evaluation will determine if (1) patterns and outcomes of cancer care management in the community change over time, and (2) whether changes can be related to the introduction of different programs and program interventions. For the programs under study, the interventions can be characterized as (1) the availability and use of clinical research protocols in the CGOP and CCOP, and (2) the development and use of patient-management guidelines in the CHOP. Since there is substantial overlap among the programs, NCI will also be able to examine the effect of combined interventions in meeting the primary program goal.

Patterns of Care Studies

The NCI is conducting a patterns of care study of elderly cancer patients. Although most cancers affect older persons disproportionately and the probability of developing cancer increases with age, relatively little is known about how the problems of old age affect cancer patient work-up, treatment, and care. Older persons in poor health often present a chronic disease complex which is long-term and severely debilitating. When cancer is linked with the chronic disabling conditions acquired during a lifetime, medical decision-making and differences in management must often be uniquely applied to older patients. Decisions are influenced not only by patients' cancer signs and symptoms, but also by their frailty; other health difficulties and chronic disabilities; and social, psychological, and economic handicaps. Advancing age, with its concomitant changes in physical ability, physiological function, and social relationships, complicates providing care to elderly cancer patients. Physicians should consider these various factors when planning cancer treatment and care recommendations for the elderly.

As a cancer control effort for the elderly, the NCI, in consultation with the National Institute on Aging, is directing a research initiative on the older cancer patient. This initiative, by stimulating the fields of oncology, geriatrics, gerontology, and other relevant disciplines and professions to conduct multidisciplinary research, is intended to reduce the knowledge gap about cancer treatment and care in the older population. Information is being sought about the natural history of cancer in the elderly, treatment patterns, the interaction of the normal and/or pathophysiological processes of aging and cancer, the overlap of intercurrent disease with cancer, and the extent to which interdisciplinary approaches may foster coordinated application of special skills for optimal cancer care for the elderly.

The assessment of the patterns of care (that is, the diagnosis, workup, staging, and treatment) for evaluation of elderly cancer patients requires an adequate data base. Research interests focus on early detection; surgical, radiotherapeutic, chemotherapeutic, or a combination of these therapies; pharmacology of cancer drugs; health professional practices; and the management of various adverse social, economic, and environmental influences.

A second patterns of care study concerns radiation therapy. The American College of Radiology is entering its ninth year of systematically assessing national patterns of care in radiation therapy. Initial and follow-up progress surveys on ten cancer sites have been completed, along with outcome surveys on six of the sites.

Four-year actuarial results have been completed for carcinoma of the cervix, Hodgkin's disease, and head and neck sites. Long-term follow-up (10-year) is continuing for carcinoma of the prostate. Final process/outcome surveys are planned for cervix, Hodgkin's disease, and larynx. This program will result in a permanent quality assurance program for radiation therapy facilities sponsored by the American College of Radiology and in improved educational strategies for upgrading radiation therapy across the country.

Rehabilitation and Continuing Care

Because of earlier disease detection and improved treatment of cancer, more people are surviving cancer than ever before. More than 3,000,000 Americans who are living today have had cancer. Rehabilitation of former cancer patients and the continuing care of those surviving with progressive disease present ongoing challenges. Rehabilitation research and continuing care are aimed at reducing cancer morbidity through the support of comparative and demonstration studies on techniques, procedures, and protocols that have specific applicability to physical, cosmetic, functional, social, and psychological problems related to cancer.

The needs of surviving patients range from psychosocial adaptation and adjustment in living with or surviving cancer to prosthesis, post-treatment, and supportive care. Continuing care research seeks to solve the problems brought on by the disease process from the initial diagnosis until death of the patient. For example, many cancer patients and their families need care and services in their homes. Rehabilitation research seeks ways to restore, to the extent possible, a "normal" life for patients and their families. For some, the disability is static and requires only a relatively fixed plan for rehabilitation; for most, the disability progresses as the disease progresses.

Emphasis is placed on projects that identify and promote optimal restorative, palliative, and continuing care methods and techniques for former and current cancer patients and for health professionals, and on stimulation of community-based participation. Support has been provided to studies that develop, field test, or demonstrate the efficacy of skills, coping strategies, and social support and to applied research on new devices and procedures. Other studies that have been encouraged address symptom control, pain management strategies, restoration and maintenance of physical function in those disabled by cancer, prosthetic and plastic reconstruction technology research, nutrition enhancement, illness behavior, and quality of life. The following are examples of activities.

- Four contracts supporting training programs for maxillofacial prosthodontists and maxillofacial dental technicians ended June 1983. These programs trained over 60 maxillofacial prosthodontists who are now capable of sharing these new ideas about orofacial restorations with other professionals.

- Current rehabilitation research addresses issues in patient compliance with cancer therapy, bone and joint replacement after tumor resection, studies in tracheoesophageal speech, and the evaluation of rehabilitation during the management of oral-pharyngeal cancer.

- Studies of pain have included investigation of its neurophysiology and a collaborative multi-institutional evaluation of the impact of multidisciplinary pain management. Data of incident pain as well as responses to treatment are being analyzed.

- Continuing care research studies have included surveillance of "cured" patients, care of patients with advancing disease, and care of patients with terminal disease.

Plans

Future research into the special needs of cancer patients for rehabilitation and continuing care will include the following topics.

- For selected aspects of cancer pain and management therapy, the transfer and utilization of optimum pain management techniques, pharmacologic studies, adherence to medical regimens, emotional support, and pain prevention (including the education of nurses, pharmacists, and physicians to recognize and physically manage cancer pain);

- Interventions to reduce morbidity and the consequences of cancer for patients and their families on social, psychological, physical, and economic dimensions;

- The influence of old age on cancer patient work-up, treatment, and care;

- Rehabilitation efforts and effects on quality of life for patients with selected cancers--head and neck, breast, and childhood cancers;

- Follow-up on findings from research conducted during the past several years on cancers of the breast, bladder, large bowel, prostate, and pancreas, to identify research initiatives incorporating rehabilitation and continuing care components.

CANCER CONTROL SCIENCE RESEARCH

The Cancer Control Science (CCS) Research activities support an integrated approach to research of cancer control applications. Primary attention is given to research on intervention strategies and their impact on populations and to research on facilitating the widespread use of proven health promotion and other cancer prevention and management techniques by health professionals, patients and their families, and the general public. CCS is also a resource for a variety of NCI technology transfer activities, including:

- Monitoring basic and clinical research activities to identify opportunities to develop and perfect new interventions to reduce cancer rates in populations, and to facilitate research on their application;

- Providing training opportunities for health professionals in order to create a national cadre of highly skilled individuals capable of identifying, researching, and applying cancer prevention and management interventions;

- Establishing program priorities, allocating resources, integrating the projects of various branches, evaluating program effectiveness, and representing the program areas in management and scientific decision-making within the NCI;

- Providing programmatic and consultative support to other divisional, institute, government, and private sector organizations that can facilitate the application of proven cancer control interventions in populations.

Two CCS components, Cancer Control Applications and Health Promotion Sciences, are described in the following sections.

Cancer Control Applications

The Cancer Control Applications component was created to ensure that research results are effectively applied o the Nation's cancer control needs in a timely manner. Thus, the program is the focal point of the NCI's efforts to work closely and cooperatively with community agencies and organizations at all levels to identify high priority cancer control problems and to stimulate quality research and programs to address them. The primary objective of cancer control applications activities is to identify opportunities for, and facilitate the application of, effective cancer control interventions. This objective is accomplished through four activity units: Cancer Control Research, Cancer Control Research Tracking, Field Applications, and Career Development.

Cancer Control Research Units

Cancer Control Research provides mechanisms for expanding the scope and improving the quality of research on cancer control interventions. The Cancer Control Research Unit (CCRU) and Cancer Control Science Program (CCSP) are the initial support mechanisms developed for this purpose. CCRUs are specialized research units, which comprise research groups who will examine the application of new knowledge in the prevention and treatment of cancers and will participate in setting national cancer control priorities. These units will require long-term support and multidisciplinary participation. They will have access to defined populations in order to measure the effect of cancer control activities. The CCSP encourages the development of core groups of researchers actively engaged in cancer control studies. These groups will complement the CCRUs.

Each CCSP will have a minimum of three cancer control research projects approved by peer review. These could include pilot projects of high scientific merit that have future promise of being supported as individual peer-reviewed research projects. Both mechanisms provide support for the development of specialized cancer control research centers provided with the expertise and resources to effect progress in cancer control research. Research conducted by these centers is to follow an orderly sequence through the five cancer control research phases. One CCRU has been funded at the Fred Hutchinson Cancer Research Center in Seattle, Washington. A multidisciplinary research program, involving a critical mass of investigators from the Center and the University of Washington School of Public Health and Community Medicine, was approved for 5 years of support. The major research focus is prevention; topics include chemoprevention and smoking cessation. The five research projects, four developmental studies, and supporting resources, which were approved, provide a well-integrated cancer control research base for the CCRU. Two CCSPs were funded in July 1983, one at the Fox Chase Cancer Center in Philadelphia, Pennsylvania, and a second at the Illinois Cancer Council in Chicago.

Cancer Control Resource Tracking

Cancer Control Resource Tracking provides an ongoing mechanism for identifying where and on what problems cancer control resources are being expended. This system will initially provide information which describes the NCI's research and program support, but will eventually be expanded to include resource allocations by State and local governments and other community organizations with cancer-related interests. This data set, when analyzed with existing disease-oriented data bases, will provide an effective means of matching cancer control opportunities with resource allocations. It can also be used to track progress as programs are developed to address significant gaps in the nation's cancer control efforts.

Field Applications

Field Applications activities build on the NCI cancer control research program and resource tracking system to identify specific opportunities for intervention and for working with national, regional, State, and/or local organizations to facilitate their applications. The Cancer Control Applications Branch (CCAB) is the focal point for developing and initiating the process by which these interactions and relations will occur. Activities draw upon the significant resources of the other programs for the technical expertise needed to jointly plan and execute programs with the various community groups.

Career Development

The Career Development unit provides educational opportunities in cancer control for health professionals, including NCI staff and cancer control professionals throughout the nation. The opportunities are varied and will include academic and research program placements and intramural programming, such as colloquia, seminars, workshops, self-teaching programs, traineeships, mid-career orientation, student internships, and small dissertation grants.

Plans

Major plans include an increase in the number of CCSPs and CCRUs leading to a greater emphasis on the Phase IV CCRUs. The major emphasis in cancer control research is on defined population studies, and the goal of the CCRUs is to encourage this type of research. CCSPs are designed as an intermediate, transitional mechanism for developing Phase IV capabilities.

Field applications will include mechanisms for working with State and local communities to encourage the development of regional, State, and local cancer control capabilities and programs which address the priority objectives and operational plans for achieving a major reduction in cancer mortality by the year 2000. The emphasis in the program is on helping communities plan and develop their own programs by providing technical assistance through technical support units, demonstrating the viability of such efforts by establishing model programs, and developing specific research studies to identify the causes for avoidable deaths from cancer and stimulating programs to eliminate those causes. The Field Applications plan proposes the initiation of several model programs and general program growth in existing technical support units and studies of avoidable mortality.

Career development offerings will be increased to meet the need for a cadre of well-trained professionals critical to ensuring the continued development of effective cancer control intervention studies and to achieving a major reduction in cancer mortality by the end of the century.

Resource tracking efforts will increase to provide for systems to track national resources applied to cancer control, specifically those related to the achievement of the NCI objectives for mortality reduction by the year 2000, and for studies of resource allocation and utilization. These activities include studies of demographic trends in the population and their effects on cancer incidence and mortality, characterization of existing resources applied to high-priority cancer sites or program activities, and area-wide monitoring of resources and their relationship to cancer control outcomes in geographic areas with population-based tumor registries. Plans are to increase funds for demographic projection studies and resource utilization, to incrementally increase existing programs, and to begin (in FY 88) the implementation phase of area tracking studies.

Health Promotion Sciences

The Health Promotion Sciences component of Cancer Control Science identifies and facilitates the applied research needed to develop, implement, and evaluate programs which reduce cancer risk, facilitate early detection and appropriate treatment, and improve the quality of life for individuals or targeted groups. The program also supports and collaborates with other NCI activities when behavioral, social, educational, or communication information expertise is required.

Health promotion science activities draw on the scientific base of four major fields of study: the behavioral sciences, social sciences, education, and communication/information sciences. Research efforts span the continuum from primary and secondary prevention to treatment and continuing care. For example, primary prevention efforts are built on the solid foundation of knowledge about health education in the school-age population. Secondary prevention efforts include studies of breast cancer detection by self-examination. Treatment and continuing care research is concerned with such issues as symptom control, compliance behavior, and patient coping strategies. The focus is the application of biobehavioral science to interventions aimed at controlling the cancer problem for the public, for cancer patients, and for their families. Following are specific activities and accomplishments of Health Promotion Sciences.

Risk Factor Intervention

Because individuals can control a number of behaviors related to cancer risk, this is an area of great opportunity for health promotion research. One project is evaluating the effectiveness of a health education curriculum in modifying the cognitive, affective, psychosocial, and behavioral factors hypothetically related to cancer risk. The inclusion of biomedical risk indicators integrates clinical and behavioral research in this 6-year, longitudinal, controlled clinical trial. Another project involves the development, implementation, and evaluation of a cancer prevention and risk reduction curriculum for students in grades kindergarten through 12. The curriculum has been selected for national dissemination by the Department of Education. Other prospective projects examining the role of behavioral factors and cancer development are expected to make significant contributions to the understanding of the behavior-cancer relationship in well-delineated populations.

Breast Self-Examination

Studies of breast cancer detection by self-examination continue to explore the effectiveness of this technique. One study examines beliefs, knowledge, and other variables that are important predictors of breast cancer detection behavior. Another longitudinal study tests the hypothesis that women practicing breast self-examination (BSE) can detect breast cancer of significantly smaller sizes at more favorable stages, thereby decreasing the likelihood of death from breast cancer, than women not practicing BSE. Early findings from this study suggest that frequency of BSE is associated with stage at diagnosis. That is, women who report more frequent practice of BSE are diagnosed in a more prognostically favorable stage. Therefore, studies are also exploring the cognitive, affective, and educational dimensions and methods to improve competence in initiating and maintaining this health habit.

Treatment and Continuing Care

The treatment issues involving cancer patients stimulate a variety of research topics relating to symptom control, compliance behavior, and coping strategies to reduce distress from the disease. The following selected projects illustrate the scope of current behaviorally oriented treatment and continuing care research.

Studies on the management of chemotherapy side effects test the effectiveness of systematic desensitization in controlling anticipatory nausea and vomiting. Other studies examine the usefulness of behavioral procedure (relaxation techniques) in reducing the aversive responses associated with nausea induced by chemotherapy. Preliminary findings suggest that the intervention reduces the adverse side effects of cancer chemotherapy in experimental groups. Other studies have focused on the safety and efficacy of various therapies in the treatment of depression, pain, anxiety, and insomnia in cancer patients.

An understanding of compliance behavior can lead to development of effective interventions to achieve optimal treatment results. Five studies currently address factors associated with noncompliance on the part of cancer patients. One of these also examines physician noncompliance to treatment protocol.

There are several epidemiologic projects which describe the social aspects of cancer, including an analysis of patterns of care received by colorectal cancer patients prior to diagnosis and during the first year of treatment. Other studies endeavor to develop a broad quantitative picture of the demographic, social, medical, and hospital factors that affect the place of death of cancer patients.

The Cancer Communications Network

The Cancer Communications Network (CCN), consisting of nearly two dozen regional offices, was established in 1976 to ensure that accurate, up-to-date information on cancer cause, prevention, early detection, diagnosis, treatment, rehabilitation, and continuing care is readily available and accessible to the public and health professionals. Each CCN office is responsible for the following services:

- Establishing and operating a toll-free telephone service (the Cancer Information Service, or CIS) for immediate access to answers to cancer-related questions from cancer patients, their families, the general public, and health professionals;
- Identifying, developing, implementing, and evaluating a limited number of special projects to meet specific cancer information/education needs within the service area;
- Developing and maintaining a resource directory of agencies and services available to cancer patients and their families within the defined service area of the center;
- Establishing a Communications Office to plan, administer, promote, develop support materials for, and evaluate activities undertaken by the contract staff.

During the past year, many significant accomplishments have taken place in the CCN. Included among these are the following:

- User Services: A new nationwide toll-free telephone number, 1-800-4-CANCER, was instituted for the Cancer Information Service on March 1, 1983. Replacing the many different WATS line telephone numbers, this new system provides national publicity and promotes the use of the service.

- User Research: A new standardized call record form will facilitate a user survey to assess (1) the degree to which the CIS is able to meet informational needs of its users, (2) the relative importance of the CIS in the decision making process of callers, and (3) the degree to which CIS contact influences the health behavior of users.

- Service Promotion: The CIS program staff cooperated with the Office on Smoking and Health of the Public Health Service to distribute a series of public service announcements featuring Dr. C. Everett Koop, U.S. Surgeon General. The Cancer Information Service telephone number was tagged on these announcements, and CIS program staff responded to resulting inquiries. The public service announcements were very successful in generating calls to the CIS from individuals who wished information on how to stop smoking.

Plans

Planning activities for new health promotion science initiatives center on selecting projects, establishing time and sequence priorities, identifying targets, reviewing prior studies, and developing performance measuring devices. Special emphasis will be placed on interventions involving school-aged children and populations at high risk for cancer to modify lifestyle practices and personal health habits related to the prevention of cancer.

To further the understanding of factors underlying the differences between blacks and whites in cancer patient survival, an epidemiologic study will establish three data collection centers and one coordinating center. The data collection centers will be population-based tumor registries with the capacity to accumulate certain minimum numbers of black patients with cancer of the breast, colon (excluding rectum), uterus, and bladder. Among the possible explanatory variables for the differences are delays that affect the extent of disease at diagnosis, host vulnerability (e.g., nutritional status and overall health status), tumor histology, and treatment patterns independent of stage at diagnosis.

Data will be collected from medical records, from pathologic review of the tumors, and from patient interviews about what brought the patient to a physician, delay in seeking treatment, family history of cancer, prior and concurrent illnesses, nutritional factors, estrogen receptor determinations, treatment compliance, socioeconomic indicators, extent of disease, and morphologic characteristics of the tumors. The findings will lead to interventions designed to narrow the survival differential between blacks and whites for the four cancer sites. It is expected that by 1990 the program will have identified and be in the process of disseminating effective interventions to the black population.

An intervention for melanoma is under consideration which will combine education for individuals at high risk with professional education and early attention to suspicious lesions. Present utilization of mammography for women over 50 years of age is about 5 percent of that population, and increasing that figure to 50 percent may significantly reduce mortality. Studies to determine which interventions for women and health professionals will improve utilization of mammography and physical examination by physicians will be initiated.

Development of activities will continue in the areas of work site interventions, primary care providers as intervenors, and psychosocial issues facing long-term cancer survivors. Community health promotion interventions will be instituted, and results from smoking research should be ready for widespread application to schools and primary care health professionals.

SURVEILLANCE

The cancer control surveillance activities of the NCI include research in the tracking and evaluation of the progress of cancer control, in identifying areas of the United States with particular cancer control needs, and identifying resources for cancer control. The Surveillance, Epidemiology, and End Results (SEER) program, under the Biometry Branch in the Office of the Director, is the major component of the system tracking cancer incidence, patient survival, and mortality for defined population areas of the United States. SEER consists of eleven population-based cancer registries covering 12 percent of the nation's population. The SEER is critical to monitoring the progress of the National Cancer Program.

This system provides data for large-scale cancer epidemiologic studies to test hypotheses about possible etiologic factors. A study underway will evaluate whether the use of oral contraceptives results in an increased risk of breast, endometrial, or ovarian cancer.

In addition, the SEER program constitutes a unique research tool for cancer control. Incidence, mortality, and survival data are being examined in an effort to identify geographical areas of the nation (or specific population subgroups) that are most likely to be in need of cancer control interventions to reduce cancer incidence and mortality, and in extending patient survival. Conversely, researchers will be able to study areas, such as Hawaii, in which cancer incidence and mortality appears to be lower than the national average. Factors associated with an improved cancer profile may be identified, and, if possible, applied to other areas.

Plans

The SEER program will be utilized extensively during the next several years, as the NCI launches its year 2000 goal of reducing cancer mortality by 50 percent. SEER data provides the best estimate of the nationwide burden of cancer and, thus, will enable researchers to monitor cancer control efforts to reduce cancer mortality through a variety of interventions.

In addition, NCI researchers will continue to utilize the SEER data in epidemiologic studies and will undertake a more detailed analysis of cancer patient survival. Factors such as extent of disease at diagnosis, tumor cell type, and method of treatment will be incorporated into survival analyses, which will serve as the basis for an ongoing assessment of improvement in cancer treatment.

Activities in tracking cancer control, that is, monitoring the progress being made in mortality, incidence, and morbidity has been largely in the province of the SEER program in the past. The new emphasis on cancer control and the setting of a national cancer control goal to reduce mortality by 50 percent by the year 2000 required that the estimates of incidence and mortality be developed from across the country, in addition to those from the SEER areas. Plans are underway to make use of the other tracking resources now available, including other population-based registries and hospital-based tumor registries. Efforts are underway to coordinate NCI activities and needs with those of the National Center for Health Statistics and of other Federal and State agencies. Resources will be allocated to support the necessary monitoring; the identification and analysis of cancer control activities across the country, including screening programs; education programs aimed at risk reduction through changes in diet or smoking behavior; programs aimed at improving the public recognition of the signs and symptoms of cancer so that the earliest possible detection can be achieved; and programs for early detection. Further research has been planned to determine methods for extrapolating from SEER data to geographical areas not covered by SEER. For example, it may be possible to estimate cancer incidence through demographically based functions derived in SEER areas and projected to non-SEER areas and supplemented by population-based surveys.

A major effort will be undertaken to track cancer control in several communities or regions to evaluate progress in cancer control activities and to acquire the appropriate data for evaluating defined population and demonstration studies of cancer control interventions. Efforts will also continue in long term tracking of breast cancer screenees, to better understand their interactions with the cancer control system and to more fully estimate the benefits of screening and the relative effectiveness of the screening modalities involved.

RESOURCE DEVELOPMENT

Conducting the NCI cancer control research and related activities depends on three types of resources: research centers, facilities, and trained personnel. These types of resources are supported by the NCI in these programs: the Cancer Centers Program, which includes the Organ Systems Program and the Construction Program, both in the Centers and Community Oncology Program; and the Manpower Development Program, under the Cancer Control Science Program.

Cancer Centers Program

Since the early 1960s, the Cancer Centers Program has provided grants for the support of programs in cancer research, cancer education, and cancer control at educational and research institutions in the United States. The purpose of cancer centers is to extend knowledge and understanding of the causes, mechanisms, prevention, detection, diagnosis, and treatment of the multiple forms of cancer through the development of either specialized or broad multidisciplinary programs in basic and clinical cancer research. The demands of modern cancer research are increasingly complex and costly; thus, providing environments conducive to interdisciplinary coordination and collaboration is an effective and economical means of providing for these needs. Centers vary greatly in size and breadth of programs. Depending on areas of existing strength, they encompass a variety of activities, from highly specialized and narrowly focused programs to broad, coordinated, multifaceted programs. As a national resource, cancer centers provide a critical core of highly trained laboratory and clinical research personnel, physical facilities and equipment, and administrative structures necessary to generate new knowledge of cancer and to accelerate technology transfer.

Although center activities are funded by both Federal and non-Federal funds, a major portion of their total financial support is from the NCI. An important funding mechanism is the Cancer Center Support Grant (CCSG), also referred to as core grants. As of July 1984, 54 Cancer Centers had active core grants, 15 of which were Laboratory Cancer Research Centers. Of the remaining 39 centers, all of which combine basic and clinical research programs, 20 have been designated as Comprehensive Cancer Centers and 19 as Clinical Cancer Research Centers.

The CCSG provides support for the planning, development, evaluation, administration, and maintenance required to consolidate and focus cancer-related activities in a single administrative and programmatic structure. The CCSG may support salaries for key professional and administrative personnel, shared equipment, special facilities and services, alteration and renovation, and developmental research activities. It is important to emphasize that, except for developmental projects, research itself is not supported by the CCSG. The CCSG provides only a minor portion of total support for the centers. The major portion of cancer center research is funded by combinations of research grants.

Cancer centers supported by core grants played a major role in many of the cancer research activities of the past year. For example, many centers are conducting oncogene research, and several are involved in research activities related to Acquired Immunodeficiency Syndrome (AIDS). Accomplishments are highlighted below.

- Two centers competed successfully for NCI support for regional clinical trials programs. Other centers are conducting evaluations of biological response modifers.

- Three cancer centers were awarded funds for the establishment of Cancer Control Science Programs and Cancer Control Research Units.

- A number of Clinical and Comprehensive Cancer Centers are serving as a "research base" for community programs participating in the relatively new Community Clinical Oncology Program.

In the past year, a review of the Cancer Centers Program was initiated for the purpose of characterizing centers according to research activities and resources. Also, a series of cancer center planning meetings was held to discuss and develop ways in which centers can collaborate or interact with one another for their mutual benefit and the benefit of their regional constituents. The President's Cancer Panel has also been addressing cancer centers' issues and will continue to do so over the next two years. The potential for expanding the role of cancer centers in the area of cancer control also was addressed, as was the feasibility of sharing resources among centers as a means of making the best use of new technologies available to some centers.

Plans

Several multicenter, collaborative efforts are under consideration for the next fiscal year, such as an intercenter research endeavor to evaluate nuclear magnetic resonance (NMR) imaging. This collaborative activity would have the potential to improve the flow of information, while limiting duplication in research efforts.

To promote and facilitate collaboration in other special research studies, an attempt will be made to more precisely characterize cancer centers and their resources.

Organ Systems Program

The Organ Systems Program, which is part of the Cancer Centers Program, consists of grant-supported projects of targeted cancer research, each a planned research effort involving cancer at a specific organ site. These projects have been concerned with cancers of the breast, large bowel, pancreas, prostate, and urinary bladder. This program was implemented by the NCI during the past decade to foster and stimulate interdisciplinary research aimed at cancers of certain organs where the level of research activity has not been commensurate with the public health problem posed by the diseases. Having attracted new investigators, the program succeeded in stimulating new research in these areas.

The Organ Systems Program is advised by five working groups: breast, large bowel, pancreas, prostate, and urinary bladder. Each working group is responsible for planning, coordinating, monitoring, and evaluating the epidemiologic, laboratory, and clinical research components of these programs. Interaction and communication among these components is fostered through workshops, conferences, and other mechanisms, as appropriate. As areas for new research initiatives are identified, they are organized into program announcements, or other research solicitations, depending on the mechanism most appropriate to achieve the program goals.

Each Organ Systems project sponsors and encourages laboratory and clinical research directed toward improving the techniques available for detecting and diagnosing, treating, and ultimately preventing or controlling cancer at the particular organ site. This charge requires the development and use of effective planning and management systems to stimulate, encourage, coordinate, and facilitate individual and collaborative investigation from all disciplines of biomedical science, while maintaining a focus on the course of disease. This is done through various forums ranging from small meetings and conferences to major workshops. Investigators are encouraged to submit grant applications to accomplish the program objectives. An extensive discussion of accomplishments and plans may be found in the Organ Systems section of the Cancer Centers Branch report.

Construction Program

New cancer research programs and the need for safe facilities for accomplishing biohazardous cancer research make provision of construction funds essential. Construction support is also needed in order that coordinated and contiguous clinical and basic research space can be provided that will permit scientists to work together rather than dispersed throughout an institution. Some programs, such as research into pi-mesons in clinical treatment, require the construction of special facilities. The intent of the Cancer Institute Research Facilities Program, initiated in 1971, is to create necessary physical resources for cancer research through Federal participation in the cost of new construction and renovation at basic and clinical cancer research facilities and for those associated with administration, service, and animal support. The construction program continues to upgrade existing buildings for laboratories and clinical research units, some of which are biohazard containment facilities. These will minimize cross-contamination and will prevent the release of potentially cancer-causing materials into the laboratory or the surrounding community.

The program provides facility support to the extramural programs of all NCI Divisions and to cancer center core activities. In addition, the program provides technical engineering and architectural services to other NIH Institutes, particularly the National Eye Institute.

The primary review and evaluation of applications is essentially scientific. Consideration is given to the scientific merit of proposed programs; the technical competence of the staff of the applicant institution; the intellectual environment of the institution; and its scientific, fiscal, and administrative capabilities. Other criteria include location of applicant institution, applicant institution's role in the National Cancer Program, promptness with which construction can be started, whether space requested is commensurate with projected program scope, net space utilization of 60 percent or more, reasonable cost, and acceptable design. The applicant institution must also demonstrate its ability to satisfy the 50 percent matching fund requirement.

Plans

At the request of the President's Cancer Panel and with the support of the Department of Health and Human Services, a project for the evaluation of cancer facility research needs has been undertaken. The objective of this project is to identify current and projected needs for cancer research support facilities. In particular, the project will categorize the research support facility needs, identify the future uses for such facilities, provide justification for such use, and provide sufficient data to allow the projected cost of the facilities to be imputed.

Currently, about 100 institutions across the United States are involved in cancer research. During the past 10 years, a total of $216 million has been expended for building and facility renovation. The stringent demands of safe chemohazard and biohazard environments, coupled with the need for sufficient laboratory and clinical facilities, require that NCI have an accurate estimate of the need for such facilities. The project will determine this estimate through the use of a facility survey.

Several surveys were made during the past 5 years to estimate the need for cancer facility construction; however, none was designed in a manner which would minimize potential bias. This survey will build on the information gathered in the past, but will couple this information with a research plan designed to minimize study bias.

Training Program

The Training Program is guided by two objectives. The first is to plan, organize, and support a national effort to provide quality cancer research training and development for fellows and trainees ranging from the predoctoral trainees to nearly established investigators. Experience can be gained in applied and/or basic science areas relevant to cancer cause, prevention, detection, diagnosis, treatment, control, and rehabilitation.

The second is to augment professional cancer education through Cancer Education Grants which encourage institutions to improve, expand, and coordinate their undergraduate cancer teaching activities, improve the continuing education of health professionals, and provide short-term research and service experiences for undergraduate students in professional schools and for prebaccalaureate minority students.

To meet these objectives, several mechanisms are used: National Research Service Awards (including research training grants and research fellowships), Research Career Development Awards, Preventive Oncology Academic Awards, Clinical Investigator Awards, and Cancer Education Grants. Each of these mechanisms is explained under the Cancer Training Branch section of the Cancer Control Science Program chapter.

Cancer Education Program

The following support during FY 84 was provided under the Manpower Development Program:

- 595 predoctorals and 715 postdoctorals (including about 700 M.D.s) were supported under Institutional Training Grants (T32). For the third consecutive year, the proportion of M.D. to Ph.D. research trainees was increased.

- Individual Postdoctoral Fellowship Program supported 190 postdoctorals.

- A short-term training course was offered on the Pathobiology of Cancer in Keystone, Colorado; 90 basic and applied research trainees and fellows who previously lacked training in the actual disease mechanisms of cancer actively participated in this course.

- The preventive oncology instructional materials derived from the 12 preventive oncology education contracts were disseminated.

- The Clinical Investigator Award was initiated to encourage more physicians to undertake careers in basic or applied research. The first applications have been received.

- Listings of available training positions for minority institutions were distributed to encourage the entry of minority scientists into cancer research.

Plans

The following activities are planned for the next fiscal year:

- Initiate a predoctoral nursing oncology fellowship under NRSA guidelines;

- Make first Clinical Investigator Awards;

- Continue development of the cancer control sciences research training grant announcement;

- Stimulate additional training applications in prevention, epidemiology, cancer control science, surgical oncology, and radiation oncology;

- Make new awards under the revised guidelines for Cancer Education Grants.

NCI Cancer Control Objectives

The NCI is establishing a set of national cancer control objectives aimed at guiding the cancer control effort toward the overall goal of reducing cancer mortality by 50 percent by the year 2000. Cancer control objectives are defined as quantitative changes in cancer incidence, mortality, and other appropriate measures of the cancer burden. These objectives help the NCI make decisions for cancer control program directions, set priorities for allocating resources between competing uses, and evaluate program progress.

Cancer control will be effected through the simultaneous use of three strategies:

- Through research, both basic and applied, to identify the means of preventing some cancers, to detect cancer early, and to evaluate effective treatment regimens;

- Through evaluation of effective technologies, and through their transfer to the practicing community through education of health professionals and the public;

- Through cancer control surveillance to identify poor mortality, incidence, or survival performance in geographic areas, specific population groups, specific cancer sites, as well as to identify cancer control successes; and to report the results in a manner useful to reshaping the cancer control program.

The analysis for setting the objectives is being performed by members of the cancer control research and practice communities and NCI staff. A report is in preparation for the National Cancer Advisory Board. The staff and consultants are organized into four groups. First, the prevention group is developing quantified objectives for public knowledge and behavior related to diet, nutrition, and smoking and thereby to cancer incidence by various sites. Second, the group addressing cancer screening and detection will formulate quantified objectives related to the early diagnosis of specific cancers, taking into account available technologies and cost-effective screening. A third group is considering treatment-related quantified objectives for morbidity and survival by cancer site or groups of sites. Fourth, a group will address cancer control surveillance and focus on recommendations for information feedback and evaluation of the cancer control plan, methods for identifying regions of the country where improvement in cancer control is possible or has been made, and, in general, recommendations on ways to track progress toward meeting cancer control objectives.

In addition to formulating objectives, the groups will identify Federal, State, and community actions, programs and initiatives geared toward meeting the objectives.

STAFF

Director:	Peter Greenwald, M.D., Dr.P.H.
Deputy Director:	Joseph W. Cullen, Ph.D.
Program Analyst:	Linda Bremerman
Program Director:	Thomas Glynn, Ph.D.
Program Director, Smoking Research Application:	James F. Callahan, D.P.A.
Special Assistant to the Office of the Director:	Margaret Mattson, Ph.D.
Editorial Assistant:	Kathleen Y. Fanning Catherine A. O'Connor
Secretarial Support:	Mary K. Gold Elizabeth Mugge Kathy Bauman Zella Linn

[illegible] AVAILABLE

Board of Scientific Counselors

The primary advisory group to the Division is the Board of Scientific Counselors, which advises the Director on matters related to the progress of the programs of the Division. This is accomplished by examining projects through the concept review mechanism, by furnishing advice on policies and planning, and by evaluating the ongoing activities. The Board provides an oversight function of the Division's intramural research.

The Board of Scientific Counselors consists of 20 members from the scientific community who are knowledgeable concerning cancer prevention, detection and treatment, epidemiology, professional training, and the application of research. Four standing subcommittees provide budget oversight and parallel the three major programs of the Division--Budget and Evaluation, Prevention, Centers and Community Oncology, and Cancer Control Science.

The full Board met in October 1983 and in January and May 1984. During these sessions, the members considered 48 concepts for proposed new projects or project renewals, and were provided with oral reports from Division staff members covering ongoing and proposed scientific programs.

Members who served on the Board during FY 84 are listed below.

Chairman: Dr. Lester Breslow*
Professor, School of Public Health
University of California
Center for Health Sciences
Los Angeles, California

Dr. Philip G. Archer
Professor of Biometrics
University of Colorado Medical School
Denver, Colorado

Dr. Erwin P. Bettinghaus
Professor and Dean
College of Communication Arts and Sciences
Michigan State University
East Lansing, Michigan

Dr. Charles D. Cobau*
Medical Oncologist
Toledo Clinic, Inc.
Toledo, Ohio

Dr. Robert A. Cooper, Jr.
Director
University of Rochester Cancer Center
Rochester, New York

Dr. Robert W. Day
Director
Fred Hutchinson Cancer Research Center
Seattle, Washington

Dr. Jerome J. DeCosse
Chairman, Department of Surgery
Memorial Sloan-Kettering Cancer Center
New York, New York

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* Term expired on June 30, 1984.

Dr. Leonard R. Derogatis*
Director, Division of Medical Psychology
Johns Hopkins Hospital
Henry Phipps Psychiatric Clinic
Baltimore, Maryland

Dr. Harry Eagle*
Director, Cancer Research Program
Albert Einstein College of Medicine
Bronx, New York

Dr. Saxon Graham
Professor and Chairman
Department of Social and Preventive Medicine
State University of New York at Buffalo
Buffalo, New York

Dr. David Mark Hegsted
Associate Director for Research
Harvard Medical School
New England Primate Research Center
Southborough, Massachusetts

Dr. Barbara M. Hulka
Professor of Epidemiology
School of Public Health
University of North Carolina
Chapel Hill, North Carolina

Dr. Loretta M. Itri
Director of Clinical Oncology
Department of Medical Oncology and Immunology
Hoffmann-LaRoche, Inc.
Nutley, New Jersey

Dr. Mary Jane Jesse
Professor and Vice Chairman
University of Miami, School of Medicine
Department of Pediatrics D-820
Miami, Florida

Dr. Kaye H. Kilburn
Professor of Medicine
University of Southern California
School of Medicine
Los Angeles, California

Dr. Laurence N. Kolonel
Director, Epidemiology Program
Cancer Center of Hawaii
University of Hawaii
Honolulu, Hawaii

Dr. Lewis Henry Kuller
Professor and Chairperson
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh
A-527 Crabtree Hall
Pittsburgh, Pennsylvania

Dr. Virgil Loeb, Jr.
Professor of Clinical Medicine
4989 Barnes Hospital Plaza
St. Louis, Missouri

Dr. Charles R. Smart
Chief of Surgery
L.D.S. Hospital
Salt Lake City, Utah

Dr. Doris Y. Wilkinson*
Professor of Medical Sociology
Howard University
Washington, D.C.

Mary E. Sears, M.D.**
Acting Executive Secretary
Blair Building, Room 614
Bethesda, Maryland

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* Term expired June 30, 1984.
** Retired June 30, 1984.

Biometry Branch

OBJECTIVES

On October 1, 1983 the majority of the Biometry Branch of the Division of Cancer Cause and Prevention (now the Division of Cancer Etiology) was transferred to the Office of the Director, Division of Cancer Prevention and Control. While the Branch continued to carry out the same general functions as it had in the past, the orientation of its activities shifted more toward cancer control. The overall objectives of the Branch are as follows:

- Conduct surveillance of cancer incidence, mortality and patient survival through the Surveillance, Epidemiology and End Results (SEER) program of population-based cancer registries;
- Design and coordinate clinical trials in cancer therapy and participate in the design of intervention trials in populations;
- Develop statistical methods for clinical trials, cancer research and cancer control applications;
- Carry out descriptive and analytic studies with emphasis on the use of data from cancer registries.

OVERVIEW

The work of the Branch is conducted by three Branch sections and the Office of the Chief. A fourth section, Computer Science, is inactive at present. During the year, the activities of the Branch focused heavily on analytical work designed to identify targets for interventions aimed at the overall NCI goal of reducing cancer mortality by 50 percent by the year 2000. The Branch is also charged with the surveillance function necessary for assessing progress toward this goal. The accomplishments of the past year are described below by Branch section.

OFFICE OF THE CHIEF

In the reorganization of the Biometry Branch, the Office of the Chief was reduced from six professionals to two. Some of the research previously carried out by this group is being continued by the Branch Chief and the remaining staff member. Work is continuing on the analysis of trends in cancer incidence and mortality. A paper presenting the basic methodology for analysis of long-term trends in cancer incidence in the United States, as applied to seven major cancers, was published during the year. Using this methodology, a monograph is now being prepared presenting both long-term and short-term trends in incidence and mortality for a large number of cancer sites.

Using a large geographic data base in a computer at Lawrence Berkeley Laboratory at the University of California, Berkeley, an analysis of the relationship between employment in various industries and the subsequent occurrence of specific cancers is being carried out. The data base is being explored to determine whether it can be used to relate other variables to the geographic analyses being carried out collaboratively in the Branch to identify target areas for intervention to reduce mortality from specific cancers.

An analysis of the relationship between alcohol consumption and the occurrence of the major cancers among Japanese men in Hawaii was completed during the year. The results were published showing a relationship between beer consumption and rectal cancer and between wine and whiskey consumption and lung cancer. Further research on these relationships is being carried out by the Japan-Hawaii Cancer Study group at Kuakini Medical Center in Honolulu.

The Office of the Chief is now exploring approaches to monitoring cancer incidence and patient survival in areas of the United States not covered by the SEER Program. It is expected that this will result in specific projects during the coming year.

DEMOGRAPHIC ANALYSIS SECTION

The Demographic Analysis Section is responsible for the planning, development, conduct and analysis of program investigations concerning the incidence of and mortality (and hence patient survival) from cancer in various population subgroups. The primary task of the section is the collection, evaluation and analysis of data from the SEER program to determine factors associated with variation in rates, associations of cancer risks with demographic factors, and the development of related methodology and statistical theory. The section has responsibility for the evaluation of data gathering and processing procedures of the SEER program, as well as for quality control of case finding, data abstracting and coding.

Surveillance, Epidemiology and End Results (SEER) Program (Z01 CN 00118 BB)

Population files for the years 1973-82 by race/ethnicity, sex and age have been developed for every county within the SEER geographic areas of coverage--approximately 12 percent of the population of the U.S. This task has been made more difficult due to the necessity of correcting for the misclassification of Hispanics into the "other than white" category at the time of the 1980 census. The staff has been in constant consultation with officials of the Census Bureau to correct the population counts by reallocating the appropriate number of persons from the "other than white" to the "white" category and to interpolate the correct intracensal estimates between 1970 and 1980, as well as to project populations for 1981 and 1982. As a result, all cancer incidence and mortality rates previously produced for the SEER areas are being recalculated on the basis of the new population estimates. Age-adjusted and age-specific cancer incidence and mortality rates for the individual years 1973-81 are being prepared for publication. These rates will update those previously published for the years 1973-77 in National Cancer Institute Monograph 57. This will be the first time that incidence and mortality data for 1978-81 will have been published although these data have been available previously on request. Preliminary incidence data for 1982 are also available.

Major emphasis of the SEER program, this year, has been the initiation of new extent-of-disease coding schemes within the program and in converting all previously collected extent-of-disease data into the staging categories of the American Joint Committee (AJC) on Cancer. The latter task has been an enormous undertaking since three different extent-of-disease coding schemes were used between 1973 and 1982. The task has been further complicated by the fact that certain categories of patients within the various AJC staging categories appear to be misplaced. For example, women with large breast tumors (>5 cm) with no nodal involvement (AJC Stage IIIA) have better survival than women with medium-sized breast tumors (2-5 cm) with lymph node involvement (AJC Stage IIB). Currently, the staff is working with various anatomic subcommittees of the AJC to correctly identify all staging categories in terms of prognosis. Once all data have been correctly staged, 1-, 3- and 5-year relative and observed survival rates by stage can be calculated by anatomic site and morphologic type of cancer for patients diagnosed in 1973-81 and followed through December 31, 1983. Survival trends can then be analyzed by comparing patients diagnosed in the early and mid-1970s with those diagnosed in the late 1970s and early 1980s.

An analysis of survival data among eight racial/ethnic groups in the United States provided cancer survival data on American Indians, Chinese, Japanese, Filipinos and Hispanics. This comparison had not been attempted previously. The data indicate that survival rates for Hispanics were almost identical to those for Anglos (Caucasians, not of Hispanic origin) except for cancers of the bladder and ovary, and Hodgkin's disease. For many primary sites, Japanese experienced the highest survival rates and American Indians the lowest. In comparison to Anglos, Japanese had higher survival for cancers of the stomach, colon, prostate and breast. Survival rates for blacks were much lower than those for whites for cancers of the corpus uteri and urinary bladder. Survival rates for Chinese and Hawaiians were roughly comparable to those for Anglos, while survival rates for Filipinos tended to be similar to those for blacks.

The staff has consulted extensively with those in geographic areas across the U.S. who are in the process of setting up population-based cancer reporting systems designed to be compatible with SEER reporting procedures. This collaboration has been realized through staff training; provision of SEER Self-Instruction manuals; supply of computer software; and critique of local manuals, materials and operating procedures. The Branch staff has been active in the local and National Tumor Registrars Associations, promoting high level tumor registry methodology at the hospital level.

In addition, the staff has participated on the international level with the World Health Organization, the International Agency for Research on Cancer, and the International Association of Cancer Registries, to promote standardized tumor nomenclature, reporting procedures and definitions. Further, there has been direct collaboration with and financial support of the activities of the Israel Tumor Registry for the purpose of comparing trends in the incidence of and survival from cancer between Israel and the United States.

BIOMETRIC RESEARCH AND ANALYTIC STUDIES SECTION

The responsibility of the Section is to conduct research in cancer epidemiology, patient survival and statistical methodology in each of these areas. In carrying out these responsibilities the Section staff utilizes data from the SEER program and other available resources such as data from the National

Center for Health Statistics. The research program of the Section includes studies of factors that may be associated with risk of developing cancer (subsequent primary cancers as well as initial ones) and studies of factors associated with cancer patient survival. The Section staff collaborates with and provides consultation to the entire Division, other Divisions of NCI as well as nongovernmental groups concerned with cancer research problems related to Section responsibilities and staff expertise.

Studies of Cancer Patient Survival (Z01 CN 00117 BB)

A study of black/white differences in cancer patient survival has been initiated in collaboration with the Health Promotion Sciences Branch. The cancer sites being studied are female breast, colon, urinary bladder, and corpus uteri. The purpose of the study will be not only to identify prognostic factors which explain black/white differences in survival, but also to identify prognostic factors which may lead to cancer control strategies resulting in better patient survival for blacks as well as whites. The study has been designed and contracts for three data collection centers and a coordinating center have been let. A total of 2,600 patients will be included in the study with the following equal numbers of black and white patients diagnosed during the period December 1, 1984 through November 30, 1986 to be included: female breast (500), colon (500), corpus uteri (150), and urinary bladder (150). Patients will be interviewed to obtain information on behavioral and nutritional factors supplementing information on extent of disease and treatment obtained from the patients' medical record and a histologic slide review by expert pathologists. The patients' physicians will be contacted in an attempt to augment information on treatment and diagnostic procedures obtained from the medical record.

A part of the strategy for the national cancer mortality reduction goal is to translate the latest cancer management methods developed in research centers to the general community. To obtain information regarding the magnitude of the gap in survival outcome between state-of-the-art therapy and general medical practice, data for patients treated at comprehensive cancer centers have been obtained from the Centralized Cancer Patient Data System (CCPDS) and are being compared with similar data from geographic areas encompassed by the SEER Program, the latter representing general cancer patient survival experience. Some analyses have been completed for Hodgkin's disease and work has begun on non-Hodgkin's lymphoma and childhood leukemia. Preliminary findings for Hodgkin's disease indicate that the CCPDS series has a higher proportion of patients in the nodular sclerosis histologic classification which is associated with more favorable survival. Also, the data indicates that CCPDS patients were younger on the average than SEER patients. Adjustment for histologic type and age indicated that CCPDS patients had somewhat better survival than SEER patients. Additional analyses will be done. Preliminary findings, however, suggest that improvement in the management of Hodgkin's disease in the community could be achieved through application of existing knowledge.

Utilizing data from the SEER program, relative survival at five years increased from 53 to 59 percent for all forms of childhood cancer for patients diagnosed during 1973-76 as compared to those diagnosed during 1977-80. Specific improvements included those for acute lymphocytic leukemia (49 to 68 percent) and soft tissue sarcoma (56 to 62 percent). No unusual increases or decreases in incidence rates of childhood cancer occurred between the periods

1973-76 and 1977-80 for childhood cancers in areas covered by the SEER program. Also, mortality rate trends were consistent with survival results, i.e., a decrease in mortality was found for all forms of childhood cancer, for children with acute lymphocytic leukemia, and for children with soft tissue sarcoma. Additionally, childhood cancer patient survival for SEER was found to be more favorable than that previously reported for childhood cancers diagnosed during 1970-73 for the following forms of cancer: acute lymphocytic leukemia, acute granulocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, neuroblastoma, and bone tumors. However, some of the latter data were from registries that are not currently included in the SEER program and/or were not population based.

Data on 1,215 patients with soft tissue sarcoma were obtained from the American Joint Committee's Task Force on Soft Tissue Sarcoma to study recurrence-free survival. The median time to recurrence was ten months. Using multivariate procedures, extension and location of the primary tumor in addition to its histologic grade were found to be important predictors of recurrence.

Data were analyzed from a randomized clinical trial conducted in the 1970s by the Breast Cancer Cooperative Group. The additive effect of vincristine (V) to cyclophosphamide (C), methotrexate (M), 5-fluorouracil (F), and prednisone (P) was tested in the treatment of advanced breast cancer. Roughly half of the 427 patients included in the trial received CMFPV and the other half received CMFP. No statistically significant differences in survival or tumor response were found for the two treatment groups, however, the group receiving V did experience significantly more CNS toxicity. Reasons for testing the additive effect of V included its known CNS toxicity and its high cost.

Descriptive Cancer Epidemiology (Z01 CN 00115 BB)

The goal of reducing cancer mortality by 50 percent by the year 2000 has prompted surveillance of the entire U.S. for geographic areas with mortality rates for selected cancers that are higher than one would expect under usual statistical variation. Colorectal cancer was selected as an initial site for this investigation, since it represents a substantial proportion of the overall cancer problem and may be amenable to interventions designed to prevent disease occurrence. Age-adjusted colorectal cancer mortality rates were computed for both sexes for each of two time periods for every county in the U.S. Counties were identified for which the county rates were statistically significantly higher than the total U.S. rate for all four sex/time-period groups. Using this procedure, 45 counties across the U.S. exhibited statistically significant excess colorectal cancer mortality. Since three of these 45 counties were within the SEER program areas (nine counties were in New Jersey, a new participant in the SEER program, but incidence and survival data were not readily available), incidence and survival data for them were readily available so that one could obtain a clue as to whether the excess mortality was due to high incidence, more advanced stage of disease at diagnosis or poor overall patient survival results. Incidence rates for these three counties were significantly higher than the overall average for the entire SEER program, while extent of disease and survival characteristics were only trivially different from total SEER. Thus, if these results held for counties not in SEER areas as well, it appears that mortality reduction interventions for colorectal cancer should be focused on prevention. A similar mortality analysis was done for female breast cancer and ovarian cancer. For breast cancer, 41 counties exhibited statistically significant excess mortality and for ovarian cancer, nine counties were listed. The incidence and survival analyses for these cancer sites must be completed before clues regarding intervention strategy will be clear. Plans for further work in this area include analysis of data for other cancer sites for which interventions would appear to be both feasible and effective.

Information on 955 mesothelioma cases diagnosed during the years 1973-80 was obtained from the SEER program. The primary site of origin was recorded as pleura for 776 cases (81 percent), peritoneum for 146 cases (15 percent), heart for 9 cases (1 percent), and other or unknown site for 24 cases (3 percent). For white males with pleural mesotheliomas, incidence increased significantly over the 8-year time period; no significant trend was observed for peritoneal mesothelioma among white males or for either pleural or peritoneal mesothelioma among white females. The average annual incidence rate for pleural mesothelioma was 9.4 cases per million among white males during 1973-80 in all SEER areas combined. Significantly higher rates occurred in areas having port cities; 15.4 for Seattle and 13.8 for San Francisco-Oakland, while residents of Iowa had a significantly lower rate of 5.5 cases per million. The median survival time for the series of SEER cases was eight months and prognosis was similar for pleural and peritoneal mesotheliomas.

No substantial temporal increases in pancreatic cancer incidence rates were observed during 1973-81 (SEER data), a marked contrast from only a few decades ago. The largest and most consistent temporal change observed was a decrease in incidence among white males. It appears that in populations with high autopsy rates, substantial numbers of pancreatic cancers will be diagnosed that would not be found in the absence of autopsy. International comparisons of pancreatic cancer incidence rates may be biased since autopsy rates vary appreciably between countries. International correlations have suggested a more important role for coffee consumption than for cigarette smoking in the etiology of pancreatic cancer. However, these studies may not be entirely valid due to higher autopsy rates in countries where coffee drinking is very prevalent, with consequently better case finding than in the U.S. and elsewhere.

Work has continued on the study of multiple primary cancers utilizing historical data from the Connecticut Tumor Registry and the SEER program. The association between the stage of two breast cancers diagnosed in the same woman was studied for 1,061 women with at least two nonsimultaneous breast cancers, with the second breast cancer occurring in the contralateral breast. A statistically significant positive association was found which is at least consistent with an immunological hypothesis regarding the effect of cell mediated immunity associated with a first breast cancer on second breast cancer behavior. A pathology slide review is currently being planned to further establish whether the association between the stages of two independent primary breast cancers in the same woman is due to immunological phenomena. Multiple primary cancers in children under age 15 years and in young adults aged 15 through 34 years are being studied using data on patients diagnosed between 1960 and 1980 from the Connecticut Tumor Registry and between 1973 and 1980 in the SEER areas. Observed and expected numbers of various second cancers will be determined, as well as possible associations of second cancer risk with treatment. The multiple primary cancer experience of all SEER registries is currently being reviewed to identify first cancer/second cancer associations. The effects of factors such as age at diagnosis of the first cancer, calendar period of diagnosis and treatment will be considered regarding significant associations which are found.

Morbidity Among Long-Term Survivors of Childhood Cancer and Their Offspring
(Z01 CN 00114 BB)

This study, done in collaboration with investigators in the Division of Cancer Etiology, was designed to detect the effects of cancer and its treatment on childhood patients who survived to adulthood, as well as any effects that might have been transmitted to their offspring. The study, a retrospective-cohort-with-sibling-control design, investigated the occurrence of subsequent primary cancers, quality of life, late morbidity other than cancer, infertility among the cases, and cancer and birth defects among offspring.

Cases selected from five U.S. cancer registries were patients under 20 years of age with a histologically confirmed malignant neoplasm or brain tumor diagnosed between the years 1945 and 1974, who survived at least five years after diagnosis, and who reached the age of 21 years. Up to two sibling controls were selected for each case with sequential priority given to full blood relationship, same sex, closest in age. Interviewer-administered questionnaires were obtained for 2,305 (91 percent) cases and 3,299 (77 percent) controls.

Even though data editing is continuing, some preliminary observations are now possible. Cancer occurred in eight (0.34 percent) of 2,328 offspring of cases versus ten (0.21 percent) of 4,789 offspring of controls. These two rates, adjusted for person-years of follow-up, were not significantly different from each other or from general population expectations. One or more major birth defects occurred in 192 (8.3 percent) case-children and 353 (7.4 percent) control children; these results were not significantly different.

The quality of life issues investigated in this study included graduation from high school (yes/no); age at graduation from high school (for those who reported graduation); marriage (yes/no); never married because of a health problem (yes/no); ever married, but had no children (yes/no); and health interference with taking a job or holding a job (yes/no). The percentages who graduated from high school were similar for cases and controls as were the ages at graduation of those who graduated. When compared with controls, higher percentages of cases reported they never married; didn't marry because of a health problem; married, had no children; or had health problems that interfered with their ability to take or hold a job.

Further analyses on these issues will introduce adjustments for possible confounders. Investigations of issues such as excess infertility and occurrence of subsequent primary cancers will be conducted.

Cancer in Oriental Populations (Z01 CN 00113 BB)

The Chinese and Japanese migrants to this country represent unique resources for epidemiologic investigations on cancer, because the majority of them are concentrated in a few major settlements, facilitating comparison of their cancer experience with that of homeland populations. In accordance with the Division-wide cancer programs being conducted in the U.S. and abroad, studies of Chinese and Japanese were initiated to ascertain the transitional effect at both geographical and generational (nativity) levels. The results will serve to provide clues to the mapping out of cancer prevention and control programs for various populations and American-Orientals in particular.

Cross-Continental Cancer Patterns

Studies on cancer among the Chinese in the U.S. have suffered in the past from the unavailability of comparable statistics on homeland populations. This limitation was largely resolved by the release of the 1975 People's Republic of China (PRC) national mortality survey data.

A study of cancer mortality among the Chinese in the United States (by nativity), Hong Kong and Guangdong Province in the PRC, was completed and submitted for publication. The project was undertaken to ascertain possible migration effects, because the majority of American and Hong Kong Chinese migrate from Guangdong. Much of the findings were most rewarding. Briefly, two distinctive patterns of displacement were discerned in relation to the site-specific risk-level noted for Guangdong and Hong Kong Chinese (GHC). Thus, for those cancers associated with high risk in the GHC population (nasopharynx, esophagus, liver, cervix and perhaps stomach), a downward transition was exhibited in American immigrant Chinese, with American born Chinese displaying a further depressed rate. In contrast, low risk cancers observed for GHC (colon, lung, breast, and leukemia) followed a different pattern, with foreign-born Chinese initially incurring a rise in mortality, and American born Chinese experiencing a lower risk.

Based on a similar hypothesis of the first study, a second project was initiated comparing cancer mortality in Taiwan Province and Singapore with that for Fujien Province, since the majority of Chinese in the first two areas came from Fujien. Preliminary findings indicate that much variation in rates was evidenced for cancer of the esophagus, stomach, liver, and lung. Only small differences appeared for colon, rectum, uterus, and leukemia. For both males and females, stomach and esophagus were the two sites showing excessive risk for Fujien as compared to Taiwan and Singapore.

Cancer Patterns in the U.S.

Incidence, mortality, and survival statistics on Chinese and Japanese groups in the SEER areas of San Francisco and Hawaii are being analyzed along with Los Angeles incidence data. Emphasis is placed on intercommunity differences as indicated below.

- Chinese: Geographic differences, most of long standing, were observed (e.g., higher rates in San Francisco than Hawaii for cancers of the lung, liver, and nasopharynx). Regardless of site-specific variations in risk level between Chinese and whites, the rank order of leading sites are similar (i.e., lung, colon and prostate for males, and breast, lung, colon, and corpus uteri for females).

- Japanese: Cancer risk differentials among the communities were reflected in generally higher rates in Hawaii than San Francisco (e.g., lung for both sexes, and stomach, prostate, bladder, thyroid, and liver among males). Though stomach cancer remains a much higher risk for Japanese than whites, the leading sites were similar for both: lung, prostate and colon among males and breast, colon, stomach (lung for whites), and corpus uteri among females.

Plans

Plans are being made to obtain 1980 data on Chinese and Japanese in the U.S. by nativity and in homeland areas, to extend the 1960 and 1970 cancer mortality analysis, thus permitting a two-decade trend analysis. The 1980 data are of particular interest because of the inclusion of a sizeable number of American born population at cancer ages. Attempts will also be made to secure local dialect data in Fujien, in order to compare them with those for different population segments in Singapore, and to discern more distinctive patterns of change in cancer mortality. The findings on site-community-specific differentials are being considered for initiation of studies of acculturation practices in relation to cancer prevention and control.

CLINICAL AND DIAGNOSTIC TRIALS SECTION

The Clinical and Diagnostic Trials Section (CDTS) is responsible for developing and assessing statistical methodology for controlled clinical trials and for field testing of diagnostic and screening techniques. In carrying out its mission, the Section provides full statistical support for selected trials, including development of the detailed study plan, collection and processing of reports, analysis of the data, and preparation of scientific papers. The Section also provides consultative services to various groups involved in NCI supported therapeutic and diagnostic trials, and as part of its research effort attempts to develop more powerful statistical techniques for analyzing trial results. Since the transfer of the CDTS Section to the DCPC in October 1983, the responsibilities of the Section and the emphasis of its program have begun to broaden and change in response to the program needs of the Division. New methodological problems are in urgent need of solution if these programs are to have the greatest efficiency in design and impact in reducing cancer mortality.

In accordance with the objectives of the CDTS program, the activities of the Section have been grouped into two main projects: (1) Statistical Methodology Research, and (2) Consultation on Clinical Trials and Other Studies. The following paragraphs outline some of the main activities underway in FY 84 under these two headings.

Statistical Methodology Research (Z01 CN 00116 BB)

Factorial Designs for Prevention Studies

Investigations have been started to explore the possibility of using factorial designs for clinical trials of agents which might prevent the development of cancer. The design of such trials presents special problems because of the large numbers of subjects which must be studied in order to obtain a sufficient number of endpoints (e.g., development of cancer) to provide reliable estimates of treatment effects. Traditionally, factorial designs have been used in agricultural and industrial applications where analysis with a linear statistical model is appropriate. Investigators are presently exploring the implications for design of non-linear endpoints such as cancer incidence (assumed to have Poisson variation) or time until development of cancer. So far it has been found that, unlike the situation for the linear model, independence of the treatment effect estimates does not hold in general, but that factorial trials may nevertheless be markedly more efficient than studying one preventive agent at a time in separate trials or in multi-arm, non-factorial designs. Further work will explore the proper analysis and interpretation of these designs, use of various incomplete factorial designs, and the effects of plausible interactions on statistical power.

Looking for Cancer "Hotspots"

This project was started in response to questions about geographic areas which have unusually high or low survival experience, or an unusual distribution of stages at diagnosis. Standard statistical methods have been adapted to answer this question. In certain cases, aggregating data from several geographic regions is necessary in order to provide sufficient cases for survival calculations. This procedure has been formalized. SEER survival experience for colon and breast cancer has been used to answer substantive questions about areas with outlying survival experience and the need for further investigation. For both cancers mentioned, several SEER areas have been identified as possible outliers. In the future, these techniques will be applied to other common cancers such as lung and uterus, and a summary of all cancers thought to respond favorably to treatment.

Analysis of Cancer Maps

The use of maps of cancer mortality has become commonplace, but special statistical methods are not generally available to deal with problems inherent in analyzing these aggregated data. In particular, geographic regions represent observations which are not independent due to the shared environment of neighboring areas. Consequently, conventional methods of statistical modeling must be changed. This project has attempted to adapt linear regression for the analysis of mortality maps in view of correlated observations. The autocorrelation of nearby geographic regions can be modeled empirically with an autocorrelation term which can be used as an explanatory variable. In this way, cancer mortality rates can be related strongly to certain geographic and demographic measures. Using lung cancer in white males and data from state economic areas, the inferences closely match those from other methods. In the future, these techniques will be applied to county level data as well as other cancers, in order to generate hypotheses about environmental causes of cancer.

Assessing Treatment-Covariate Interactions

A statistical test has been developed which determines whether treatment A is better than treatment B in some subsets of patients in a clinical trial and worse in other subsets. This disparity is called a qualitative interaction, and it has much greater clinical significance than mere variation in the strength of treatment effect. Classical statistical tests of heterogeneity are designed to detect the latter phenomenon.

Sample Size Calculations for Case-Control Studies with Quantitative Exposures

New procedures have been developed for calculating needed sample size for case-control studies with continuous exposures, rather than for simple dichotomous exposure classification. These methods are being applied to design studies on serum micronutrients.

Tests for Trend

When potentially prognostic factors are screened to identify predictors, clever grouping of adjacent factor levels may occasionally give evidence of a trend relating prognostic factor and outcome. The distribution of the largest slope of outcome on prognostic factor (used as a test of trend) among all the slopes obtained by grouping prognostic factor levels has been studied. A slope apparently significant at the 5 percent level, may be, in fact, only significant at 12 percent if the largest slope has been chosen.

Planning for Intervention Studies in High Risk Groups

Groups of patients at high risk for developing a particular cancer are often chosen as the target population for intervention studies because more events will be observed in a fixed period of time, greater benefit may be expected, and ethical problems with the use of new treatments are somewhat minimized. A particular problem in the design of such studies is to compute the needed sample size, given that the disease rates are higher than those which would be obtained from population incidence figures. By using data from case-control studies, patients at various levels of risk may be identified and in some situations their numbers in the general population may be estimated using formulas related to attributable risk.

Interactive Data Analysis Programs

The Clinical and Diagnostic Trials Section continues to support a series of interactive computer programs for analyzing clinical trial data, and new features are continually incorporated into this package. During FY 84, a powerful and versatile linear regression program was adapted to the conversational format and added to the system. This system increases our capacity to respond efficiently to requests for sophisticated data analysis. Although designed primarily for data from clinical trials, these programs have proven useful for a variety of applications requiring data processing operations such as recoding, tabulation, and selection of records, as well as statistical analyses including computation of descriptive statistics, screening of variables for prognostic significance, contingency table analysis, logistic regression, and both unadjusted and adjusted survival analysis. These programs have been used increasingly for the specialized data analyses performed by members of the Section, by other NIH scientists, and by workers at other centers. Some of these programs have recently been implemented at the statistical office of the National Surgical Adjuvant Breast Project in Pittsburgh and at the Data Center of the European Organization for Research on Treatment of Cancer in Brussels.

Consultation on Clinical Trials and Other Studies (Z01 CN 00119 BB)

Lung Cancer Clinical Trials

The Section provides full statistical support for the Lung Cancer Study Group. This group of five major medical centers was formerly supported by contract with the Division of Cancer Treatment (DCT), but has recently been successful in competing for continued support under a cooperative agreement. The activities of the group will be expanded to include 11 protocols in lung cancer and accrual of some 350 patients per year. The primary emphasis of these protocols is the study of adjuvant chemotherapy, radiotherapy, or immunotherapy in patients with resected lung cancer. Currently, patients are accruing to nine protocols, two protocols are in the followup phase, and two replacement protocols are being developed. Results from several of these protocols provide evidence that combined chemotherapy (cytoxan, adriamycin, cis-platinum) may prolong survival in patients with non-small cell lung cancer. A study of adjuvant intrathoracic BCG in patients with resected non-small cell lung cancer revealed no benefit from this form of immunotherapy. Radiotherapy is under investigation in several protocols. Recently, protocols have been developed to evaluate the role of surgery following a course of chemotherapy and/or radiotherapy designed to render inoperable patients operable. The Section is responsible for preparing extensive analyses and statistical tabulations for all active protocols semiannually.

Brain Tumor Clinical Trials

The Section provides full statistical support for the activities of the Brain Tumor Cooperative Group. This group currently consists of seven medical centers which conduct randomized Phase II and Phase III clinical trials of treatment for malignant glioma. The group has been in existence since the late 1960s as a contract-supported activity of DCT. In 1983, the group successfully competed for continued support from DCT under a cooperative agreement. Currently there are two protocols accessioning patients. The Phase II study compares PCNU with intracarotid cis-platinum in patients who have not previously received chemotherapy or who have non-progressive tumors, and compares interstitial radiation with interferon in patients who have failed on chemotherapy. The Phase III study is a 2x2 factorial trial comparing intravenous versus intracarotid BCNU with and without added intravenous 5-FU. In addition, patients are being followed on two other protocols. During FY 84, final analyses were carried out on three completed Phase II studies involving eleven different drugs.

Testicular Cancer

During FY 84, the Section continued its responsibility for study design and analysis of the Intergroup Study of Testicular Cancer, a nationwide randomized trial comparing adjuvant combination chemotherapy versus chemotherapy use only for relapses. Stage I patients are also being followed to determine factors that may predict which tumors will recur. By May 1984, 203 patients had been admitted to the randomized trial, and 244 Stage I patients were being followed. During FY 84, several updated analyses of factors prognostic for nodal involvement or recurrence were performed and reported at scientific meetings. Responsibility for this project is being transferred to DCT statisticians at the end of the fiscal year.

Serum Marker Studies for Breast Cancer

Serum and background information have been collected from over 11,000 women for evaluation of biological markers for breast cancer. Samples from 6,300 asymptomatic normals and 3,000 women with benign breast disease, most with documented two-year, disease-free followup, as well as 1,500 breast cancer cases, are available. The first serum drawing occurred in 1977 and the availability of this resource to qualified researchers was announced last year. Several requests have been evaluated and blinded panels of serum have been sent. The Section is responsible for the collection, editing and analysis of all data, and for providing an updated inventory of material in the serum bank.

Multiple Markers for Diagnosing Lung Cancer

Section members in collaboration with the NCI Diagnosis Branch are analyzing a series of serum panels of twelve biochemical assays from patients with benign lung disease and with various stages of lung cancer. Initial analyses showed the anticipated diagnostic value of CEA (carcinoembryonic antigen) as a marker. A careful search for potentially useful marker combinations showed that CEA and total sialic acid work well together. This result was achieved using both logistic discrimination and using a new statistical method, the "recursive partitioning algorithm." The performance of this marker combination was been assessed on independent serum samples. Future work will consider the relationship between tumor marker levels and the extent of disease.

Makari Skin Test

The Section has been providing statistical support for two studies of the Makari Skin Test. The first evaluates the test as an aid to diagnosis, and the second determines the prognostic value of the test in predicting subsequent recurrence of disease after surgical resection of colorectal, lung, and breast cancer. These studies, sponsored by the Stauffer Chemical Company, are being conducted in several collaborating medical centers in the U.S. and in England with the assistance of the Laboratory of Immunodiagnosis, NCI. As of May 1984, 250 patients had been entered into the diagnostic protocol and followed for at least one year after initial diagnosis. The test did not discriminate between patients whose biopsy revealed cancer and those without cancer. Even after a one year period to allow emergence of "hidden" cancers, the test failed to discriminate. Various modifications to the test evaluation criteria did not improve performance.

Hospice Study

DCPC-sponsored contractors have completed a prospective, longitudinal examination of hospice care and services for terminal cancer patients. Two papers concerning the analysis of these data have recently been completed. The first provides a general description of the characteristics of hospice patients, some indication of their survival experience, and uses stochastic process methods appropriate for the analysis of longitudinal data to trace patient trajectories from hospice entry to death. The second paper describes an analysis of data on physician evaluations of hospice patients' pain. Intensity, persistence, and the time when severe pain was first (if ever) reported are related to patient-specific features such as age, sex, primary disease site and physical condition upon hospice entry and used to define groups at enhanced risk of early or long-lasting severe pain.

Psychological Aspects of Breast Cancer

DCPC-sponsored contractors performed a controlled, prospective study of the psychological impact of radical mastectomy. In the analysis of the results, large numbers of psychological scales were replaced by a relatively few principal components. MANOVA methods were then used to examine changes in these components over the year of the study. A paper submitted for publication relates how mastectomy patients showed much more psychological distress soon after surgery than control group members (who had less sexually threatening or less surgically mutilating interventions), but returned to control group levels by the end of the year.

Prognostic Analysis of SEER Melanoma Data

In conjuction with the DCE, a survival analysis has been performed on SEER data for 5,714 melanoma patients. The study was to examine prognostic features which are available for the first time among such a large number of patients. The large number has been exploited to divide the data into two parts, one for model development, and the other for validation. This second phase provides an estimate of how well the model will predict among new patients; this is inaccessible if the same data are used for model development and testing. Melanoma surface area, thickness, extension, and the Clark's index are shown to be powerful predictors of survival time.

PLANS

During the coming year, the Biometry Branch will continue to maintain a strong program in descriptive cancer epidemiology through the SEER program and related studies. This will serve not only to provide further clues to cancer etiology and a basis for monitoring cancer control efforts, but it will also provide a basis for continued collaboration with the epidemiology branches in the Division of Cancer Etiology.

More intensive work will be carried out in at least two major areas related to cancer control:

- Development of a complete surveillance system for monitoring progress toward the year 2000 goal by implementing some of the recommendations developed in the NCI effort to establish cancer control objectives;

- Development of statistical methodology specifically oriented toward population intervention trials and collaboration on the design of such trials and analysis of results.

STAFF

Branch Chief:	Earl S. Pollack, Sc.D.
Section Chief:	David P. Byar, M.D.
	Max H. Myers, Ph.D.
	John L. Young, Jr., Dr.P.H.
Cancer Expert:	Wai Y. Tan, Ph.D.
Computer Specialist:	Valerie D. Van Holten
Computer Systems Analyst:	Donald K. Corle, M.S.
	Mary M. Cusano
	M. Darlene Naughton
	Vivian F. Pelham
Mathematical Statistician:	Benjamin F. Hankey, Sc.D.
Medical Record Librarian:	Betty Jean Cicero
	Jack B. Cunningham
	Mary A. Kruse
Senior Staff Fellow:	Steven Piantadosi, M.D., Ph.D.
Medical Statistical Investigator:	Mitchell H. Gail, M.D., Ph.D.
Research Sociologist:	Haitung King, Ph.D.
Senior Investigator:	David L. Levin, M.D.
Statistician:	John W. Horm, M.S.
	Constance L. Percy, M.S.P.H.
Statistician (Health):	Sandra C. (Steinhorn) Abbott, M.S.
	Ardyce J. Asire, M.S.
	Anne Baranovsky, M.S.
	Roger R. Connelly, M.S.
	Herman W. Heise
	Frances B. Locke, M.S.
	William I. Lourie, Jr., M.P.H.
	Lynn A. (Gloecker) Ries, M.S.
	Evelyn M. Shambaugh, M.A.

Staff Support:	Caroline A. Ball Varnetta A. Bush Josephine I. Davis Elizabeth B. Davison John Kelly Gloria E. Fleming Cynthia Fournier Mary Krause Barbara A. Lyles (Marie) Julie Paolella

Operations Research Branch

OBJECTIVES

The Operations Research Branch (ORB), organizationally placed in the Office of the Director, contributes to the Division Cancer Control Research program in analytic disciplines related to cancer control, including statistics, operations research, epidemiology, and computer science. The Branch also serves as the focus for the Division's program evaluation activities. The current organization includes four sections: Biostatistics, Cancer Control Epidemiology, Screening, and Computer Systems.

The overall objectives of the Branch are:

- To plan and conduct research related to the tracking of cancer control including research on the optimum allocation of resources to control, and the use of cancer control data to identify problems in cancer treatment, prevention and early detection;
- To plan and conduct a comprehensive program of research on research methods related to cancer control, particularly the impact of diet on cancer; methods of dietary assessment; design of large scale Phase III, IV and V clinical trials; and data management in large scale studies;
- To plan and conduct research related to cancer screening and detection focusing on development of evaluation methods for screening modalities;
- To evaluate major NCI programs related to cancer control including, for example, the Community Clinical Oncology Program (CCOP) and the information system for physicians, PDQ (Physician Data Query);
- To provide comprehensive analysis, operation research, biostatistics and computer systems support and guidance to the Division.

OVERVIEW

ORB has grown considerably over the past years both in program and in personnel. The Branch name was changed during the year to Operations Research Branch from Biometrics and Operations Research Branch to reflect a change in responsibility with the addition of the Biometry Branch to the Division. As an intramural branch the majority of the Branch research is included under the headings of specific research projects, briefly abstracted in the remainder of this chapter. The range of research underway includes: the development and evaluation of dietary assessment methods, particularly important to the Division prevention research programs; the analysis of National Health and Nutrition Examination Survey (NHANES) data as part of efforts to identify the role of diet in cancer incidence; analysis of cancer incidence data in each large population to identify the potential impact in those populations of cancer control trials; and evaluation of screening methods for breast, cervix, bladder cancers and other sites as well as research on analysis methods related to lead time bias, survival and other issues.

A number of other activities are underway that include evaluation studies of the CCOP and the PDQ, development of program tracking systems for the cancer centers programs and for Division grants and contracts, mathematical modeling of cancer control and extensive consultation with Division staff on biostatistics, operations research, experimental design, and other topics.

During the past year, the Operations Research Branch has served as the coordinating unit for the Division's activities related to the NCI year 2000 goal to reduce cancer mortality by 50 percent by the turn of the century. Toward that end, the Division, aided by panels of NCI, other HHS, and non-Federal experts, has undertaken an effort to set stepwise, quantitative objectives in the areas of prevention, screening and treatment. Achievement of these objectives will represent a marked reduction of cancer mortality. Along with the setting of objectives, a series of recommended actions are being formulated to guide their achievement.

In addition to prevention, screening and treatment objectives, specific targets also are being set in the area of cancer control surveillance. This coordinated approach will enable the Division not only to establish a comprehensive data base detailing national cancer control activities, but also will allow an evaluation of the impact of cancer control efforts. A draft plan will be submitted to the NCI Director in late 1984, with a final report to be presented to the National Cancer Advisory Board shortly thereafter. It is expected that the Operations Research Branch will continue to coordinate the Division's activities towards achievement of each of the objectives, and will be responsible for a comprehensive evaluation of the impact of these efforts toward achieving the year 2000 goal.

The following research and program activities were underway during FY 84.

CANCER SCREENING RESEARCH

Research in Cancer Screening Methodology and Modeling (Z01 CN 00105 ORB)

The focus of this project is the development and refinement of statistical procedures for the design and analysis of screening, detection, and related studies in cancer. Statistical problems under investigation include sample size determination, comparison of analysis methods, and development of monitoring techniques and stopping rules for screening trials. Each of these problem areas is common to screening and prevention trials in which the Division participates, but the methods for screening studies must address the special lead time and length biases inherent in screening programs.

The research includes investigation of techniques to estimate and adjust for screening biases in the analysis of survival data, and study of the relationship between long-term mortality and short-term outcome measures, such as stage shift. Various approaches to analysis of survival data of breast cancer cases detected in a screening program are being investigated to examine the length bias and selection bias phenomena and their impact on the assessment of screening effectiveness. Probabilistic models of disease and screening are being developed to aid in the interpretation and evaluation of data from screening programs. A breast cancer screening model relating tumor doubling time to survival is being developed in collaboration with the Biostatistics Branch of the Division of Cancer Etiology (DCE). Characteristics of case-control studies in the context of screening evaluation are under consideration. Areas of study include definition of cases and controls, determination of appropriate exposure intervals, and influence of screening biases.

Studies in Cancer Screening (Z01 CN 00106 ORB)

Data from several cancer screening studies are being analyzed to gain a better understanding of the impact and consequences of such screening in various population settings. The results can be used by the NCI in establishing cancer control policy. These data bases also provide the opportunity for the testing and development of new techniques for data analysis. Results from the Health Insurance Plan of New York (HIP) breast cancer screening trial continue to indicate a long-term reduction in breast cancer mortality. In collaboration with the Biostatistics Branch, DCE, long-term case survival patterns and covariables are being related to population mortality measures to further assess the nature of the screening benefit. Patterns of cause of death among breast cancer cases are being studied to distinguish between postponement of death and cure.

In collaboration with the International Agency for Research on Cancer (IARC), ORB staff is analyzing the cervical cancer screening programs in Scandinavia and Aberdeen, Scotland. The objective is to estimate false negative rates and natural history characteristics and to relate these to the varying screening frequencies and delivery mechanisms in the participating countries.

In collaboration with DCE, data from the Bladder Cancer Screening Program at the DuPont Company are being analyzed to relate disease characteristics and outcome to cytology and blood tests, smoking history, and exposure to benzidine and beta-naphthylamine. With DCE and the National Institute of Occupational Safety and Health (NIOSH), updated follow-up data are being collected in a study of sputum cytology screening for lung cancer among uranium miners. The relationships among cytology classification, radiation exposure, smoking history, lung cancer, and mortality data will be analyzed. Participation in an International Union Against Cancer (UICC) screening evaluation project resulted in a monograph on methodologic issues in screening, as well as an evaluation of lung, bladder and oral cancer screening. An examination of issues in cervical cancer screening is in progress.

In addition to the above projects, ORB staff have been involved in various advisory and consultative roles in NCI during the year. Consultation on screening projects has included examination of screening for melanoma and testicular cancer, consideration of studies using a monoclonal antibody marker for ovarian cancer, and advice on uses of data and data analysis for the Breast Cancer Detection Demonstration Project (BCDDP). Staff has also worked with NCI divisions to develop the NCI-wide Detection and Diagnosis Plan.

DIETARY ASSESSMENT RESEARCH

Methodologic Studies of Dietary Assessment (Z01 CN 00110 ORB)

A number of projects are in progress to evaluate and improve the reliability and validity of dietary assessment. These include those described in the following sections.

Health Habits and History Questionnaire

In an effort to enhance the comparability between trials conducted by the Division and ensure the collection of data on important variables in a standardized manner, a questionnaire was developed. For the dietary component, both the list of foods and the associated nutrient values were developed in a data-based approach, using the NHANES II dietary intake data on a representative sample of approximately 12,000 individuals.

The questionnaire was pretested, piloted with basal-cell carcinoma trial patients (Z01 CN 00103 CPSB), and reviewed by a panel of experts. The modified questionnaire was then examined for its ability to produce results similar to those of a diet diary, with respect to vitamins A and C, total calories, fat and percent of calories from fat. This provided a favorable evaluation of the adequacy of the food list, the precision of median nutrient values, and the utility of a small-mediumlarge approach to portion sizes. Parametric and rank order correlation coefficients of the order of 0.8 were obtained.

Validation Studies

A workshop of leading researchers, convened by DCPC, urged that the Health Habits and History Questionnaire be evaluated in different population subgroups. Several field validations are planned or underway, in collaboration or cooperation with investigators at other institutions, using a variety of different populations and different reference methods. These include comparison with a diet history interview in breast cancer and colon polyp populations; comparison with several-day food records in a well population at high risk for skin cancer; comparison with multiple 24-hour recalls in an ill cancer patient population; and comparison with objective evidence of food use in a normal Southwest population. In addition, the questionnaire assessment of vitamin supplement usage will be validated against detailed product information obtained from the actual supplement bottles brought to a clinic interview.

Improvement of Nutrient Estimation in Quantified Frequency Questionnaires

A tool for nutrient estimates for use with the Health Habits and History Questionnaire has been developed in a data-based manner; median nutrient densities for each food item on the questionnaire reflect the nutrients actually consumed by the U.S. population, based on the NHANES II data. In addition, standard portion sizes to be assumed for each food item were also developed in a databased manner, reflecting actual population small, medium and large portions as observed among the 12,000 NHANES II respondents. Further improvements in nutrient estimation are expected to result from the identification of portion sizes separately for each of several age and sex groups.

Data Management and Dietary Analysis

A complete data management system, including updating, range edits and dietary analysis, has been developed to accompany the Health Habits and History Questionnaire. Coding and analysis are rapid and inexpensive.

Retrospective Dietary Assessment

This project will assess whether or not it is possible to gather accurate information about an individual's past dietary intake. The study makes use of subjects who provided multiple seven-day records seven to fifteen years ago. Their ability to provide information about their diet during that time period will be evaluated using both an interview and a selfadministered questionnaire.

U.S.-Finland Dietary Assessment Validation and Reliability Studies

The U.S.-Finland Beta-Carotene, Alpha Tocopherol Lung Cancer Prevention Trial (Z01 CN 00100 CPSB) will monitor dietary intake of these and other potentially important nutrients in over 16,000 high-risk men over several years. Two self-administered dietary survey instruments have been developed; one an extensive dietary history questionnaire with a color booklet for portion sizes, and the other a brief frequency questionnaire to monitor changes in diet. Reliability and validity studies have been carried out on both these instruments. For the validity studies, the reference method is the average intake from 12 two-day diet records collected over a sixmonth period, in 200 men. The reliability studies consist of three administrations of the instrument, conducted over two different seasons, permitting the evaluation of reliability both in the same and in different seasons. These studies provide support for the validity and adequacy of the dietary instruments used in this large lung cancer prevention trial.

Impact of Improved Precision of Carotenoid Analysis on Estimated Risk Levels in Epidemiologic Studies

The Diet and Cancer Branch will support the analysis of various retinoids and carotenoids in the U.S. food supply, in order to improve the data base on these components and permit the examination of their separate effects on cancer incidence. The Operations Research Branch, in collaboration with the Division of Cancer Etiology, will compare the results of case-control studies using the standard information on total carotenoids with the results using the newer HPLC information on specific carotenoids.

Consumption of Foods and Supplements Potentially Related to Cancer

(Z01 CN 00111 ORB)

An estimated 30 percent of all cancers may be related to diet. The National Health and Nutrition Examination Surveys (NHANES I and NHANES II) provide dietary data on a large representative national sample. Extensive organization and recoding of these data have resulted in a readily accessible data base permitting the analyses described below.

Nutrient Sources in the U.S. Diet

This project provides a quantitation of the contribution of specific foods to each of 18 nutrients. For methodologic uses, this permits the identification of foods which could be omitted because of the infrequency of their consumption. For cancer control, this approach permits the identification of foods which may be appropriate targets of societal intervention, and provides persuasive data for policy makers or the public. It demonstrates, for example, that beef is the largest single contributor of fat in the U.S. diet, providing 18-20 percent of total saturated fat.

Sources of Cancer-Associated Nutrients (Vitamins A, C and Fat) in Different Population Subgroups

This project will identify and quantify the sources of these nutrients in demographic or geographic subgroups. It will provide information with which to improve dietary assessment in subgroups, and may shed light on demographic differences in cancer incidence.

Population Consumption of "Protective" or "Harmful" Foods

While the public is becoming increasingly aware of what constitutes a healthful diet with respect to cancer, there is less awareness of the extent to which actual eating habits conform to those recommended. The NHANES II data are being used to estimate the proportion of Americans consuming foods such as dark green leafy and deep yellow vegetables, fruits and vegetables rich in vitamins A and C, cereals high in fiber, red meat, fish and fowl. Statistical analyses will be done by race, sex, broad age groups, and poverty index, as permitted by the data. The project will provide information which may be useful in dietary interventions and public information campaigns.

Demographic and Behavioral Correlates of Vitamin Supplement Usage

Patterns of vitamin supplement usage are being analyzed by demographic and behavioral characteristics, in a large representative national sample. Preliminary analyses have demonstrated, for example, a strong sex difference in supplement usage after control for other factors such as age and education. Such information may assist in understanding of demographic differences in cancer incidence or survival.

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DESIGN AND DATA MANAGEMENT OF CLINICAL TRIALS

Data Management and Design of Clinical Trials for Cancer Prevention and Control (Z01 CN 00109 ORB)

Research on these topics is prompted by the fact that large scale, long-term controlled trials will be conducted by the DCPC Prevention and Cancer Control Science Programs during the next decade. Several activities important for the design, data management and implementation of the current intramural trials in skin cancer and lung cancer prevention, in addition to broader research in controlled trials methodology, have been undertaken during this fiscal year.

Development of Sample Size Determination Methodology for Prevention Trials

This project is adapting existing methods of sample size estimation to cancer prevention trials. Subjects entering these trials may have preexisting cancers and thus not be susceptible to the intervention. Their cases, if included as trial outcomes, will result in an underestimation of the true intervention effect. Prescreening before trial entry may remove some of these cases. Since no screen is perfect, their effect can be mitigated, but not eliminated. It appears that in the context of prevention trials, sample size will always have to be increased; the greater the dilution effect, the greater the increase in sample size at the planning stage.

Methods of calculating sample size to compensate for the dilution effect have been developed for the case when the proportions test is appropriate. Expected event rates are dependent on estimates of disease prevalence, incidence in the screened population, screening test sensitivity and specificity. The cases of Poisson rates and survival analysis (using the Mantel-Haenszel test) will be considered.

A major thrust of this project is the concomitant development of a cost model which allows overall assessment of the costs of screening compared to the costs of a larger sample. Consideration will be given to the costs and benefits of combining screening and prevention trials.

Incidence of Basal Cell Carcinoma in a High-Risk Population

This study was designed to estimate the incidence of a new basal cell carcinoma (BCC) in a "high-risk" population, i.e., individuals already exhibiting previous basal cell carcinoma lesions. The study is important for two reasons. Although rarely fatal, basal cell carcinomas comprise over 25 percent of the total number of new cancer cases annually (excluding carcinomas *in situ*), and impact significantly on the U.S. medical care system. Secondly, results from this study provide confirmatory evidence to support an estimate of the incidence of new BCCs used to plan sample size requirements for a randomized double blind multiinstitutional chemoprevention trial, currently being conducted jointly with the Prevention Program (Z01 CN 00103 CPSB).

The patient population for the incidence study was drawn from a local military medical center with an active dermatology clinic. Data were abstracted from dermatology pathology log books covering a three year period. Using this study design and life table analysis methods, it was found that 18 percent of 1,059 patients developed new or recurrent BCCs during this interval, with an average of 1.5 years of follow-up per patient. An upper limit on the estimate of new tumors is 13 percent per person-year, without respect to number of tumors in the past. A preliminary estimate of the one year incidence rate of new tumors for patients with two or more tumors at a previous visit was approximately 30 percent. Thus, an estimate of the annual incidence of new BCC tumors for a high-risk population is reasonably bracketed by 13 percent through 30 percent.

The incidence of new non-recurrent BCCs was found to increase with the number of previous BCCs and with age, factors which are confounded. Additionally, the rate was found to be higher for males than females. Limitations in the quality of information available in dermatology and surgical pathology logs, and the unavailability of medical records, precluded further investigations of other risk factors using this research approach. Additional analyses of the data, utilizing regression techniques to look at the joint effect of multiple factors (age, number of previous BCCs and sex) on incidence, are in progress.

Data Coordinating Center

The Operations Research Branch is acting as the Data Coordinating Center for the "Use of Isotretinoin in Prevention of Basal Cell Carcinoma" chemoprevention trial mentioned above. The data management and coordination responsibilities include:

- Randomization of study subjects to intervention groups;
- Design and development of data collection forms;
- Production of a detailed manual of procedures and operations;
- Preparation and administration of a training program for both the study coordinators and the principal investigators;
- Centralized data acquisition, processing and management including quality assurance aspects of data and study endpoint determination;
- Monitoring systems for drug flow;
- Timely reporting and documentation of study data including reporting to the Data Safety and Monitoring Committee;
- Collaboration in the interim and final analyses of study data.

Pilot Studies for Intervention Trials

Pilot studies are a major component of large intervention trials, since the feasibility of many aspects of the large trial must be tested in a small scale study, before launching into a study with anywhere from 2,000 to 20,000 patients. The pilot study "Use of Isotretinoin in Prevention of Basal Cell Carcinoma," completed in FY 84 demonstrates some of these parameters. This pilot study was conducted in two clinics over a four month period. The objectives of the pilot were to: (1) monitor patient recruitment and enrollment; (2) evaluate local and central data management and study logistics; (3) monitor shortterm toxicity and its effect on the "blind," on patient safety and on patient compliance; and (4) to test new or modified study forms. The pilot study also revealed the importance of an orientation for study coordinators and principal investigators.

A pilot study for the "U.S.-Finland Beta-Carotene, Alpha Tocopherol Lung Cancer Prevention Trial" was planned and initiated in FY 1984. Objectives of this study are quite similar in scope to those mentioned for the basal cell carcinoma prevention trial. However, implementation of the full-scale trial is much more complex due to recruitment of over 16,000 participants; coordination of several population registries to identify and notify prospective participants; and coordination of scheduling, data management, drug flow, and quality assurance.

Plans

Plans for data management and study design methodology research include: feasibility testing of microcomputer technology for data capture at local clinical sites; evaluation of systems in terms of costs, ease of use, and quality and timeliness of data; development of micro-processor software for onsite data editing and assistance in conducting the trial; and utilization of technological developments in computer networking. Research is also planned on study design and sample size estimation for prevention trials, such as trials with chemopreventive agents or dietary interventions. Since traditional designs may require enormous sample sizes (some in excess of 100,000 subjects), alternative designs are under exploration to enable implementation of such studies in a scientifically sound manner, yet within feasible operational and fiscal constraints.

PHARMACOKINETIC STUDIES

Design and Analysis of Pharmacokinetic Studies of Selenium (Z01 CN 00108 ORB)

Selenium, a possible cancer preventive agent, is being considered for use in intervention trials. Two studies in collaboration with the Cancer Prevention Studies Branch (CPSB), are being conducted in cooperation with the U.S. Department of Agriculture to provide information on the bioavailability and pharmacokinetics of selenium in its prototype forms-sodium selenite (inorganic form) and selenomethionine (organic form). This information is necessary to the determination of time and manner of administration. The initial study, the Selenium Pharmacokinetics Study, is in progress. Kinetic modeling of both substances is underway, in collaboration with the Laboratory of Mathematical Biology of the NCI. Parameters such as percent absorption, maximum concentration, and half-life will be estimated for a single dose and compared in both fasting and nonfasting subjects. A second study, the Selenium Chronic Supplementation Study, will examine and compare the effects of multiple dosing on the absorption, distribution, and excretion of these two forms of selenium and a placebo. The Operations Research Branch, in cooperation with CPSB, functions as a data collection center and has primary responsibility for study design and data analysis requiring complex statistical methodology and use of sophisticated modeling software.

CANCER CONTROL EPIDEMIOLOGY

Development of Cancer Control Epidemiology and Tracking (Z01 CN 00109 ORB)

The purpose of this project is to develop the methodology of cancer control epidemiology, with special emphasis on its analytical models, its data tracking needs, and its foundations in biological, statistical, and epidemiologic theory.

A number of specific research initiative are either underway or planned under this project. Almost all of these efforts involve collaboration with staff outside of ORB.

Cancer control field studies are underway in collaboration with State and local officials and researchers to identify potential causes of high incidence or mortality, or relatively low survival. The emphasis in this analysis is on identifying data sources and analytical methods that can lead to assessment of the state of cancer control in defined geographic areas. In addition, the potential role of the National Death Index as an outcome measure in cancer prevention trials is being explored.

To more fully understand the interaction of cancer causes and preventive factors, a project using mathematical modeling and computer simulation is underway. The modeling is being used to estimate the characteristics of effects and measure trends as functions of demographic and biochemical factors. If such models prove feasible and accurate, they would be extremely useful in clinical trial design.

An investigation is underway to predict the effects of a cancer control intervention (e.g., a chemopreventive agent) upon the age-specific trends of cancer incidence in a population at high risk of developing cancer. The analysis is based on biologic models of carcinogenesis (e.g., multistage models). The predictors will be tested in a variety of data sources, including the results of an intervention trial of the efficacy of beta-carotene on lung cancer incidence in smokers. The relationships of such biologic models to epidemiologic interaction models will be examined.

The drawing of conclusions and inferences is important in any scientific study, but particularly so in cancer control in which the research efforts are closely related to potential practice. In this technically-oriented project an examination of the forms and use of logic in epidemiologic inferences is being undertaken. Bayesian methods, classical statistics and logical inferential systems are being examined in the context of potential cancer control studies.

A project is planned to develop predictive models to estimate the impact of cancer control interventions upon large well-defined populations. Simulation models will be developed to examine the manner in which such populations (e.g., Phase IV study populations: occupational populations, entire U.S. counties, members of health maintenance plans) represent the populations from which they were selected (e.g., State or national).

An additional project relates to assessment of knowledge, attitudes and beliefs associated with cancer control, important factors in assessing the state of cancer control. In conjunction with an extensive article on cancer prevention facts and strategies, readers of a large national publication were given the opportunity by the publisher to complete and return a survey on their attitudes and behavior before and after reading the article. Topics of the survey included their beliefs about their ability to reduce their own risk of cancer; probable changes in their dietary and smoking habits; participation in mammograms and breast self-examination; and demographic data. Results of this survey will assist in the evaluation of the effectiveness of mass print media campaigns in changing attitudes and behavior with regard to cancer prevention.

Analysis of the Breast Cancer Detection Demonstration Project (BCDDP) is continuing. Specific analyses include: factors affecting screening examination compliance, a study of screening project center differences, and a comparison of project detected incidence rates to SEER rates in overlapping areas.

COMPUTER SYSTEMS

The ORB computer systems activities during the past year have emphasized support of ongoing research efforts. In addition to providing operational support for a remote facility of the NIH main Computer Center, the Computer Systems Section has provided consultative support regarding computer science problems to DCPC investigators and systems analysis and programming support for specific projects. The latter include assisting with the data management system for the Core Data project within the Operations Research Branch and several efforts in cooperation with the Centers and Community Oncology Program such as: development of a Patient Log system for capturing and analyzing basic information regarding patients seen at the Community Clinical Oncology Program (CCOP) facilities; revision of a data base containing administrative and scientific data characterizing each CCOP and provision of interactive update and query facilities; and initiation of a similar data base for the Cancer Centers Program.

To supplement the use of the NIH mainframe computers, a program for the introduction of personal computers into the DCPC environment was planned and initiated. These personal computers will be used for scientific computing activities, administrative data processing, graphics, word processing, and telecommunications. As one of the first applications to run on the personal computers, a user-friendly data base system has been designed to incorporate basic administrative, budgetary, and scientific information regarding all DCPC Projects, Grants, contracts, and cooperative agreements. The system supports the production of routine reports regarding the projects as well as special reports and ad hoc requests.

The future program in computer systems will not only continue to emphasize support but will also begin development of modeling systems for cancer control for use by DCPC staff and others in analyzing cancer control data. Also included will be efforts to make cancer data even more accessible to staff, other scientists, and public health officials.

ANALYSIS AND EVALUATION

The past year saw the continuation of a major program evaluation effort--the evaluation of the CCOP Program in cooperation with the Centers and Community Oncology Program--and the launching of two new efforts: analytic support for the year 2000 goal-setting process and the development of a plan for evaluation of PDQ. The CCOP evaluation is fully described in the Centers and Community Oncology portion of this report.

The involvement in developing analysis tools for modeling prevention, screening and treatment program impact on incidence and mortality for the year 2000 goals were undertaken collaboratively with members of ORB, other branches in DCPC, and Dr. David Eddy of Duke University. Dr. Eddy developed a prototype model and has been working with ORB and other staff on developing projections of mortality in the year 2000 from objectives suggested by the National Plan Development Committee. In the future, the staff will be entering such models to use as planning tools for a variety of functions critical to DCPC, including the planning and evaluation of research programs. In addition, modeling the effects of cancer prevention and control programs will allow more detailed discussion of resource allocation decisions within DCPC.

Cost-benefit and cost-effectiveness analyses of cancer control efforts will be another emphasis within the Operations Research Branch. This year research on the cost-effectiveness of prevention programs was initiated and over the next year it is expected to be expanded. Also to be expanded is the effort just begun to evaluate the PDQ information system. In providing state-of-the-art information to physicians, PDQ has the promise of speeding the diffusion of research advances to practice, and the evaluation of the system is critical to realizing this premise.

PLANS

The plans for the Operations Research Branch for FY 85 are predicated on continuing the analytic research necessary to put into effect the National Cancer Institute Cancer Control Program. ORB will continue its efforts in screening research, in dietary assessment, in clinical trials, in mathematical models related to chemoprevention and diet and nutrition, and in computer systems. Particular emphases will include: the development of cancer control models to improve the prediction of the impact of cancer control efforts and to allow the division to better understand the impact of alternative allocations of cancer control resources. In cooperation with the Biometry Branch, the Operations Research Branch will identify the data and analysis needs to be supplied by a cancer control surveillance system. The Branch will also be involved in identifying populations with excessively high mortality, or low survival, for both cancer control surveillance research and potental intervention.

STAFF

Branch Chief:	Edward J. Sondik, Ph.D.
Chief, Screening Section:	Philip C. Prorok, Ph.D.
Medical Systems Analyst:	Thomas A. Marciniak, M.D.
Statistician:	Robert Conner, D.Eng. Larry Kessler, Sc.D. Blossom H. Patterson, M.A.
Biostatistician:	Brenda K. Edwards, Ph.D. Anne M. Hartman, M.S.
Epidemiologist:	Janet Sobell, M.S.
Senior Staff Fellow:	Douglas Weed, M.D., Ph.D.
Staff Fellow:	Gladys Block, Ph.D. Allen R. Feldman, M.D., M.P.H.
Computer Programmer:	Calvin Hollingsworth Gloria Rasband
EIS Officer:	Millicent Eidson, M.A., D.V.M.
Statistical Assistant:	Oscar Chavez
Epidemiology Trainee:	Bruce Trock, M.P.H.
Secretarial Support:	Lillian Tauber S. Gayle Marwine Patricia Achy Lisa Carter

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Administrative Management and Planning Branch

The Administrative Management and Planning Branch (AMPB), which is located in the Office of the Director, provides administrative and management support services for the entire Division. Within this area of responsibility, the Branch:

- Coordinates the grant and procurement cycle, and assists in development of the five year plan;
- Supports and assists in the preparation of the DCPC budget formulation;
- Provides personnel and human resource development services within the Division;
- Ensures the provision of financial management and fiscal execution of the Division.

Provision of these services is accomplished through the staff organization of the Branch. Each DCPC program (CCO, CCS, and Prevention) has an AMPB Administrative Assistant who coordinates Division efforts with those of the individual programs. Through this operational structure, the dissemination and collection of information required for effective Division management is achieved.

Using the same administrative approach and the centralized information resources, the Branch also serves as a liaison for financial management and administrative support services to the NCI.

STAFF

Administrative Management and Planning Branch:

Administrative Officer: Nicholas Olimpio

Deputy Administrative Officer: Debra Steverson

Liaison Administrative Officer: Damian Crane

Administrative Assistant, Biometry & OD: Berit Connor
Administrative Assistant, PP: Gloria Rogers Bruse
Administrative Assistant, CCSP & ORB: Elaine Zastrow
Administrative Assistant, CCOP: Gretchen Jolles

Budget Assistant: Robin Levi

DCPC Librarian: Selena L. Abrams

Support Staff: Evelyn Fine
Linda Chandler
Bonnie Jorgensen
Julie Kemp
Paul Kendrick
Linda Gaylord
Marvin Brown
Melanie Long

Board of Scientific Counselors:

Executive Secretary (Acting): Carlos E. Caban, Ph.D.

Support Staff: Nola Alpert

Program Coordination Activities

The Office of the Director also serves a coordinative role for two NCI-wide programs--Smoking, Tobacco, and Cancer, and Diet, Nutrition, and Cancer. Brief descriptions of these programs follow.

Smoking, Tobacco and Cancer Program

OBJECTIVES

The NCI Smoking, Tobacco, and Cancer Program (STCP) serves as the focal point for NCI's research, disease prevention, and health promotion activities related to tobacco use and cancer. Although responsibility for programmatic research and control activities rests with several NCI Divisions and offices, central coordination of the STCP is provided by the Office of the Director, Division of Cancer Prevention and Control (DCPC), where the broader emphasis on cancer control research is administered. The primary objective of the STCP is to decrease the incidence of cancers caused by, or related to, smoking and the use of tobacco products.

OVERVIEW

As an NCI-wide coordinated program the activities of the STCP are wide-ranging. These activities may be summarized within six broad categories.

- Basic Research: Research in this area emphasizes scientific investigations concerning the biomedical, epidemiological, and sociobehavioral aspects of tobacco usage. Included are research activities aimed at acquiring a better understanding of: (1) the role of tobacco use in cancer etiology; (2) tobacco carcinogenesis; and (3) the mechanisms underlying tobacco use behavior.

- Intervention Research: This area of activity involves the development of intervention activities which have the ultimate purpose of reducing the incidence and/or prevalence of smoking and tobacco use. It includes research to determine optimal intervention strategies for reducing the incidence and/or prevalence of smoking and tobacco use in a measurable way and research on methods for efficiently implementing these strategies; assessment of the efficacy and practicality of such intervention strategies for large populations; research to determine how, whether, and to what extent proposed interventions are effective for defined populations; and demonstration of those intervention strategies proven to be effective.

- Target Populations Initiatives: Research in this area focuses on identifying and intervening with target populations in which the greatest tobacco-related cancer prevention and control gains can be expected. Included are those populations with: (1) higher incidence and/or prevalence of smoking and tobacco use; (2) higher prevalence of combined exposure to tobacco and other known carcinogens; (3) higher dosage of exposure to tobacco; and/or (4) higher rates of incidence and mortality from tobacco-related cancers (currently or potentially).

- Surveillance: A key aspect of the STCP's activities is its capability to monitor and assess the patterns and trends of tobacco use and progress in preventing and controlling such use. Emphasis is placed on: (1) identifying those populations to which interventions need to be targeted; (2) obtaining information from major national/regional surveys on smoking to monitor patterns and trends in tobacco use; (3) applying mechanisms to determine the appropriate and timely passage of intervention studies along the cancer control research phases; and (4) developing measurable goals and objectives for tobacco-related cancer control and tracking progress toward the accomplishment of those goals and objectives.

- Information Dissemination: The development, synthesis, and communication of information concerning the cancer risk of tobacco use and means of reducing that risk, are crucial components of the STCP strategy. Program efforts include: (1) communicating through public, professional, and patient channels the specific progress being made to reduce cigarette smoking; (2) synthesizing and disseminating available information on smoking prevention and cessation; and (3) developing messages and materials specifically designed to encourage smoking prevention and cessation among individuals at high risk for cancer.

- Liaison Activities: The STCP has a responsibility to coordinate the scientific aspects of its activities with other Federal and non-Federal organizations involved in related efforts. These activities include direct collaboration with other research-oriented organizations and regular interaction and information-sharing at meetings with complementary organizations, as well as with those whose missions are diverse, but whose service areas may overlap with the STCP.

ACCOMPLISHMENTS

Although the STCP coordinates the activities of a number of NCI units, including epidemiologic and etiologic research through the Division of Cancer Etiology and public information and research dissemination through the Office of Cancer Communications, the primary emphasis of the Program is placed on carrying out controlled intervention trials, conducting defined population studies and, where feasible, developing demonstration programs through the Division of Cancer Prevention and Control (DCPC).

In FY 84, the STCP moved from a planning-only phase to a planning and intervention research phase. Accomplishments were focused in three areas: review and funding of intervention research programs, issuance of Requests for Applications (RFAs), and broad and special-topic planning meetings.

- **Intervention Research Program Funding**: As a result of special topic planning meetings held in late 1982 and 1983 with over 100 extramural scientists, health administrators, and interested individuals in the private sector, RFAs on the following topics were issued in 1983 and reviewed in early 1984: School Based Intervention Programs for Youth Smoking Prevention, Self-Help Strategies for Smoking Prevention and Cessation, Roles of Physicians and Dentists in Smoking Prevention and Cessation, and Use of the Media in Smoking Prevention and Cessation.

  One hundred and six applications were received across these RFAs, with a total request of over $192 million. Review of these projects was in March 1984 and 18 awards, totaling approximately $33 million over the next five years, were made in the following progams:

-- Youth Program

Principal Investigator	Institution
Anthony Biglan, Ph.D.	Oregon Research Institute
Brian Flay, Ph.D.	University of Southern California
David Murray, Ph.D.	University of Minnesota
Arthur Peterson, Ph.D.	University of Washington
Ernst Wynder, M.D.	American Health Foundation

These projects will complement the following school-based smoking prevention projects already ongoing in the STCP: Gilbert Botvin, Ph.D. (Cornell University), C. Anderson Johnson, Ph.D. (University of Southern California), and Steven Schinke, Ph.D. (University of Washington).

-- Self-Help Program

Principal Investigator	Institution
David Abrams, Ph.D.	Brown University
Sheldon Cohen, Ph.D.	Carnegie-Mellon University
Steven Fortmann, M.D.	Stanford University
Deborah Ossip-Klein, Ph.D.	University of Rochester
Victor Schoenbach, Ph.D.	University of North Carolina

These projects will complement the following self-help projects now ongoing in the STCP: Michael Cummings, Ph.D. (Roswell Park Memorial Institute) and James Prochaska, Ph.D. (University of Rhode Island).

-- Physician/Dentist Program

Principal Investigator	Institution
J. Allan Best, Ph.D.	University of Waterloo
Thomas Coates, Ph.D.	University of California, San Francisco
Stuart Cohen, Ph.D.	University of Indiana
Thomas Kottke, M.D.	University of Minnesota
Judith Ockene, Ph.D.	University of Massachusetts

-- Media Program

Principal Investigator	Institution
Karl Bauman, Ph.D.	University of North Carolina
Alfred McAlister, Ph.D.	University of Texas
Roger Secker-Walker, M.D.	University of Vermont

These projects will complement the following media-based STCP project: Brian Flay, Ph.D. (University of Southern California).

Each of these intervention research programs will be coordinated and monitored so that useful results be made available for Phase V study as soon as possible.

- Requests for Applications: As a result of the 1982-83 planning meetings, the following RFAs were issued in 1984: (1) Prevention and Cessation of Smoking among U.S. Black Populations, and (2) Prevention and Cessation of Smoking among U.S. Hispanic Populations. These projects, for which approximately $14 million has been committed for the next five years, will focus on the development of interventions focused on blacks and Hispanics since these populations are at high risk for development of smoking-related cancers and smoking initiation respectively.

- Planning Meetings: During 1984, the STCP sponsored a number of planning meetings. These were focused on smokeless tobacco use, smoking prevention and cessation among women, economic analysis of tobacco production and consumption, and the cessation of smoking among heavy smokers. As a result of these meetings, concepts were brought to and approved by the DCPC Board of Scientific Counselors on economic analysis, women and smoking, and smokeless tobacco use. A concept on heavy smokers will be brought to the Board early in 1985.

Plans

Plans for FY 85 include the following:

- Award of up to 10 projects focused on smoking intervention among U.S. black and Hispanic populations;

- Issue intervention-oriented RFAs on smokeless tobacco use and women and smoking;

- Participation in a contract with the World Health Organization, analyzing the economic costs and benefits of tobacco production and consumption in selected developing countries, and the potential impact of the tobacco-related actions of these countries on U.S. consumption patterns;

- Coordinate and monitor the research within each of the currently funded STCP research areas to establish as much comparability as possible among projects and make useful findings available as early as possible for widespread dissemination, particularly in light of the year 2000 goal;

- Establish final plans for the development of a controlled intervention trial aimed at heavy smokers, the group among whom the greatest cancer mortality might be expected to take place in the year 2000;
- Continue program planning, particularly in relation to the year 2000 goal.

The focus on women is especially vital for the year 2000 goal because lung cancer has already surpassed breast cancer as the primary cancer site among women in many regions of this country. If the trends of increased smoking in young women continue, lung and other smoking-related cancers will become of even greater importance as a target for mortality reduction. A focus on blacks and Hispanics is particularly important to the NCI year 2000 goal, since tobacco related cancers among both these groups is expected to increase through the year 2000.

STAFF

Coordinator:	Joseph W. Cullen, Ph.D.
Program Director for Smoking Research:	Thomas Glynn, Ph.D.
Program Director for Smoking Research Applications:	James F. Callahan, D.P.A.
Staff:	Gayle Boyd, Ph.D. Betty Lee Hawks, M.A.
Secretarial Support:	Eve Scovel

Diet, Nutrition, and Cancer Program

The Associate Director, Prevention Program, serves as the Coordinator for the Diet, Nutrition, and Cancer Program (DNCP) for the NCI. This coordination is accomplished by periodic meetings involving nutrition representatives from each of the Divisions of the NCI and the Office of Cancer Communications, and by ad hoc consultations with specific representatives as needed. The DNCP coordinator represents the NCI at the NIH Nutrition Coordinating Committee and other government-wide nutrition related activities. Noteworthy accomplishments in FY 84 include:

- Preparation of the FY 83 Diet, Nutrition and Cancer Status Report, which summarizes nutrition research supported by the NCI;

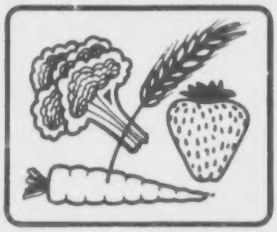
- Participation in the development of the FY 83 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training;
- Coordination with NIADDK of the third annual meeting of the directors of the Clinical Nutrition Research Units;
- Participation with NIADDK and NIA in the second release of the RFA for Clinical Nutrition Research Units for new units to be funded in FY 85;
- Presentation of progress reports on the Nutrition Research Plans of NCI at the meetings of the NIH Nutrition Coordinating Committee;
- Presentation to the NIH Nutrition Coordinating Committee of a report on International Nutrition research supported by the NCI;
- Presentation of "The National Cancer Institute's Plans for Nutrition and Prevention Research" to the Prevention Committee, NIH;
- Participation with other Institutes in release of a program announcement on research on obesity;
- Participation with NHLBI and FDA in funding the International Food Composition Data system (see Diet and Cancer Branch report for details).

STAFF

Associate Director: William D. DeWys, M.D.

NCI Staff Members:
Elizabeth P. Anderson, Ph.D., DCPC
Ritva R. Butrum, Ph.D., DCPC
Harry Canter, DEA
John Cooper, Ph.D., DCE
Rosemary Cuddy, RAAB
Colette Freeman, Ph.D., DCBD
Alice C. Hamm, OCC
Freddie A. Hoffman, M.D., DCT
Seoras Morrison, Ph.D., DCBD
Lionel Poirier, Ph.D., NMSLCC
John Shubert, Ph.D., DRG
Carl Smith, Ph.D., DCE

Prevention Program



Associate Director's Report

The Prevention Program leads DCPC's activities in advancing the knowledge base to reduce the risk of cancer. The overall Program objectives are:

- To reduce cancer incidence through applied research in the areas of chemoprevention and diet;
- To reduce cancer incidence through the development and testing of intervention strategies in occupational settings;
- To reduce cancer morbidity and mortality through research on early detection of cancer.

The five branches of the Program are: Chemoprevention, Diet and Cancer, Cancer Prevention Studies, Occupational Cancer, and Cancer Detection.

The Chemoprevention Branch supports the study of natural or synthetic micronutrients to prevent, inhibit or reverse one or more stages of carcinogenesis. The Diet and Cancer Branch concentrates on the identification of dietary factors that inhibit cancer initiation or promotion, and encourages and supports research on the development of valid dietary assessment methodologies. The Cancer Prevention Studies Branch is the intramural arm of the Program, and conducts a focused research program on cancer prevention, including studies done on a collaborative basis with other Federal and international research institutions. The Occupational Cancer Branch is continuing collaborative efforts with NIOSH to test the effectiveness of primary intervention strategies and medical surveillance in work settings in reducing cancer risk. The Cancer Detection Branch is responsible for research on methods of screening and early detection of cancer, and their impact on the reduction of morbidity and mortality in high risk populations.

New staff members have been recruited and are actively involved in developing new research. Although the staff continues to monitor and direct existing programs, it has been heavily involved in initiating and developing concepts for new research, and in formulating, developing and implementing long-range plans.

Three working groups with membership from other operating units of DCPC and the NCI complement the work of the Prevention Program staff through collaborative efforts in focusing research applications and developing research guidelines. This process provides DCPC and the NCI with a broad-based perspective for decision-making with respect to cancer prevention and control activities that cut across program and divisional lines.

These Working Groups are:

- Diet, Nutrition, and Cancer, which is coordinated by the Associate Director, Prevention Program, DCPC, is composed of representatives from each of the Divisions of the NCI. The group coordinates all diet and nutrition efforts in the NCI.
- The Chemoprevention Working Group, chaired by Dr. Charles Boone, is staffed by members of the Prevention Program, as well as by representatives from the Operations Research Branch, DCPC, and the Laboratory of Chemoprevention and the Chemical and Physical Carcinogenesis Branch, DCE. The working group coordinates NCI efforts in chemoprevention.
- The Occupational Cancer Working Group, under Dr. Kenneth Chu, coordinates occupational studies throughout DCPC. It is composed of members representing the Occupational Cancer Branch; Chemoprevention Branch; Health Promotion Sciences Branch; Smoking, Tobacco, and Cancer Program, Office of the Director; Operations Research Branch; and Research Facilities Branch within DCPC.

MAJOR INITIATIVES

During FY 84, the Prevention Program staff took major steps in implementing the previously developed plans of research flow in the Division's cancer control research phases. This effort, for both Diet and Nutrition and Chemoprevention research, led to the development of a series of new projects in different research phases. Patterned after the NCI's drug development process, the plan ensures that risk reduction clinical trials proceed with the same scientific rigor employed in therapeutic trials.

Because DCPC is launching a concerted effort of clinical testing of chemopreventive agents, guidelines on evaluating the safety, toxicity and efficacy of these agents were implemented by Program staff in consultation with the Food and Drug Administration. All chemoprevention projects, to be conducted intra- or extramurally, were reviewed by the Safety and Protocol Review Committee using these guidelines.

Work has continued on the development of research plans for Detection and Diagnosis and for Occupation and Environmental Cancer. Planning for the former is a collaboration between the Detection staff of DCPC and the Diagnosis Branch, Division of Cancer Biology and Diagnosis. The planning for Occupation and Environmental Cancer is a collaboration between staff of DCPC and the NCI Division of Cancer Etiology.

ACCOMPLISHMENTS

Specific activities and accomplishments are described in the report of each branch. A few of the major initiatives and accomplishments for FY 84 are highlighted below.

- Twenty extramural chemoprevention trials are being supported. Five of these are new awards in response to an RFA; seven are investigator initiated grants and three are funded through the Cancer Control Research Unit (CCRU) program.
- Two new clinical intervention studies of chemopreventive agents were started in the intramural Cancer Prevention Studies Branch, one in Finland, and the other in China.
- Two major clinical trials in diet and breast cancer were initiated by the Diet and Cancer Branch.
- An International Food Composition Data System was initiated.
- Applications for grants for studies of modification of eating behavior and cancer prevention were solicited.
- An occupational cancer clinical research network was established.
- Studies of chemopreventive agents in animal models were initiated.
- Phase I human studies of chemopreventive agents were initiated.
- Research on the development of analytic methods and analysis of dietary fiber was initiated.
- Strategies for radiation dose reduction for mammography and CT scanning were commenced.

PLANS

Planning for FY's 85 and 86 research directions has been started, and a number of new studies are being prepared for concept reviews. In FY 84, 30 concepts were presented by the Prevention Program to the DCPD Board of Scientific Counselors for approval. Of these, 26 were approved, three were deferred, and one was disapproved. The FY 85 plans include the development and issuance of requests for applications (RFA) and contract proposals (RFP) for the approved concepts. Projects will be supported by grants, contracts, or cooperative agreements.

Scientific activities planned for the next fiscal year are described in the Branch reports following this section.

STAFF

Associate Director:	William DeWys, M.D.
Branch Chiefs:	
Cancer Detection:	Richard Costlow, Ph.D.
Occupational Cancer:	Veronica L. Conley, Ph.D. (Acting)
Chemoprevention:	Winfred Malone, Ph.D., M.P.H.
Diet and Cancer:	Ritva R. Butrum, Ph.D. (Acting)
Cancer Prevention Studies:	William DeWys, M.D. (Acting)
Working Group Coordinators:	
Chemoprevention:	Charles Boone, M.D., Ph.D.
Diet and Nutrition:	William DeWys, M.D.
Occupational Cancer:	Kenneth C. Chu, Ph.D.
Prevention Program Staff:	
Program Analyst:	Elise W. Mackie
Administrative Assistant:	Gloria Rogers Bruse
Secretary:	Barbara B. Shepherd
Editorial Assistant:	Carlina M. Steel

Chemoprevention Branch

OBJECTIVES

The growing body of basic evidence on the inhibition of cancer and the epidemiologic evidence that cancer incidence is affected by intake of specific food groups and micronutrients, suggests that chemoprevention merits an aggressive research effort. Potential chemopreventive agents include several naturally occurring substances found in many foods, such as vitamin A and its precursor beta-carotene, vitamins C and E, and the trace metal selenium. Other agents now being studied in the laboratory include various retinoid analogues, antioxidants from several chemical classes, protease inhibitors, prostaglandin synthesis inhibitors, and trace metals. The thrust of the Chemoprevention Branch is to determine, in animal models and human clinical trials, whether these natural or synthetic agents can lower cancer incidence.

The objectives of the Chemoprevention Branch include:

- Identify and characterize agents with proven activity in preventing carcinogenesis in animals and/or preventing malignant transformation in vitro,
- Identify agents based on epidemiologic studies,
- Conduct efficacy and toxicologic testing of such agents to select the most promising,
- Conduct Phase I and Phase III Clinical Trials of potential chemoprevention agents,
- Apply research results to the general population.

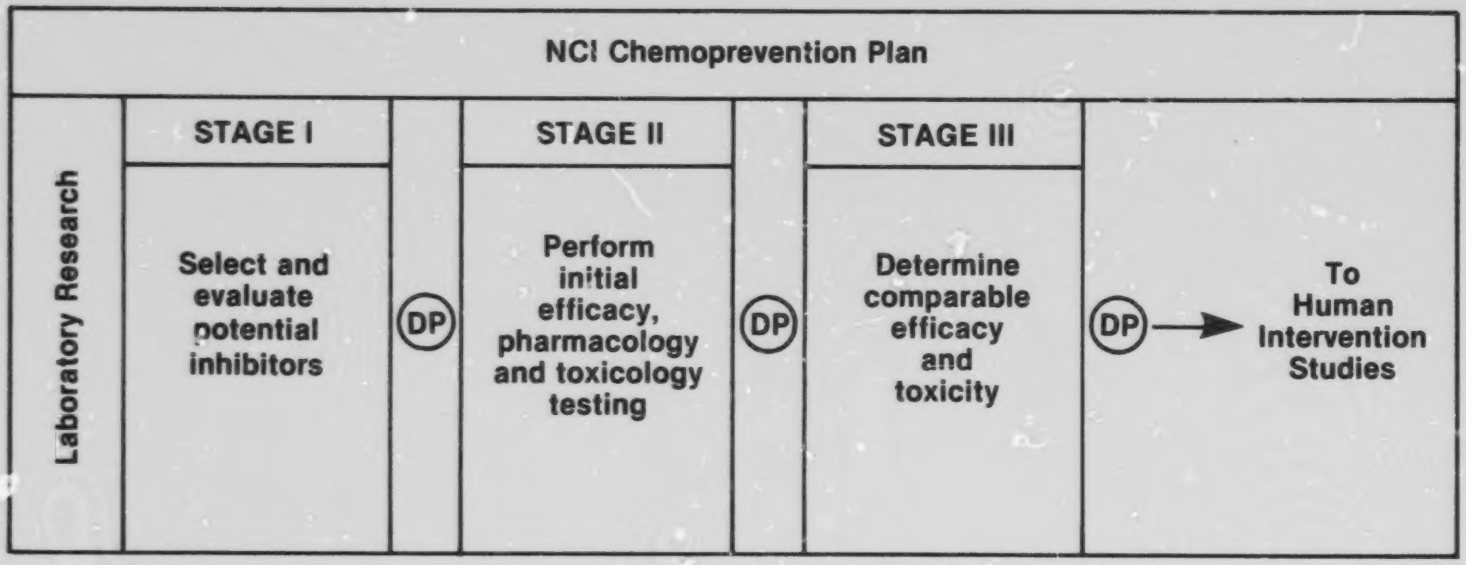
Both laboratory research and research involving human subjects help to achieve these objectives. The various Laboratory Stages of the chemoprevention plan are shown in Figure 7. The Human Intervention Stages are shown in Figure 8. These figures display the flow of research activities from one stage to another, with decision points between stages.

OVERVIEW

A number of laboratory and clinical studies provide the basis for current and planned activities in the chemoprevention program. In one of the earliest laboratory studies in 1955, Lasnitzki showed that precancerous changes in mouse prostate cells grown in vitro and treated with the carcinogen methylcholanthrene, could be inhibited by vitamin A. Subsequently, Sporn, et al., at the NCI, showed that the incidence of carcinogen-induced mouse bladder tumors could be significantly reduced by feeding the animals an analogue of vitamin A, 13-cis retinoic acid.

FIGURE 7

Laboratory Research Stages


NCI Chemoprevention Plan
Laboratory Research
STAGE I
Select and evaluate potential inhibitors
DP
STAGE II
Perform initial efficacy, pharmacology and toxicology testing
DP
STAGE III
Determine comparable efficacy and toxicity
DP
To Human Intervention Studies

DP = Decision Point
EP = Evaluation Point

FIGURE 8

HUMAN INTERVENTION STUDIES STAGES

NCI Chemoprevention Plan									
STAGE I		**STAGE II**		**STAGE III**		**STAGE IV**		**STAGE V**	
Evaluate clinical, laboratory, and epidemiologic findings	DP	Establish dose and safety for humans	DP	Conduct human trials for efficacy and safety	DP	Conduct research on applications and populations	DP	Implement demonstration programs in target populations	EP

DP = Decision Point
EP = Evaluation Point

Sporn's group also demonstrated that the incidence of carcinogen-induced rat mammary tumors could be reduced to as low as one-fifth the expected incidence by feeding synthetic retinoids after carcinogen exposure. Boutwell and his colleagues at the University of Wisconsin have also shown that synthetic retinoids inhibit the promotion of skin cancer in mice. These are just a few examples; the recent world literature includes over one hundred published studies indicating efficacy of retinoids in cancer prevention in animals. Laboratory data in general are consistent in various animal models and across animal species, indicating potential for human benefit. The chief aim of this laboratory research is to develop inhibitors of carcinogenesis which have a strong protective effect and low toxicity. Of particular interest are agents which act on various stages of the carcinogenic process, with particular emphasis on the late stages of promotion which would provide the most immediate potential benefit in human trials.

Evidence from epidemiologic and laboratory research supports the role of several micronutrients as inhibitors of various stages of the carcinogenesis process. In epidemiologic studies, persons whose diets were high in various micronutrients had a lower incidence of certain cancers, especially breast, colon and uterus. In animal studies, the incidence of certain cancers (including skin, breast, and bladder) can be reduced by increased intake of specific micronutrients, such as retinoids.

Extensive laboratory studies show that several rodent skin, bladder, trachea and breast tumors can be prevented by synthetic retinoids, including 13-cis retinoic acid, probably by control of epithelial differentiation during the promotion phase of carcinogenesis.

Among the compounds receiving emphasis at this time is beta-carotene, which is a 40-carbon molecule and a precursor of 20-carbon retinol (vitamin A). The data from human epidemiological studies, though limited, suggest that beta-carotene may protect against carcinogenesis. Two prospective cohort studies have shown an inverse association between cancer incidence and ingestion of vegetables containing large amounts of beta-carotene. The first, in Japan, indicated that the risk of lung cancer among those who ate carotene-containing vegetables less than daily, was 1.4 times that of those who ate such vegetables every day. Significant negative associations in this group were also observed for stomach and prostatic cancer. A study among Norwegian men also showed an inverse relationship between an index of beta-carotene ingestion and lung cancer. Those at the bottom third of the population with regard to carotene ingestion, had three times the incidence of lung cancer compared to those in the top third.

Several hypotheses have been developed to explain these effects. Beta-carotene could have a direct effect on cell differentiation, i.e., suppression of malignant transformation in initiated cells. It could protect against carcinogenesis by its well known effect of quenching singlet oxygen. The high affinity for singlet oxygen might prevent free radical formation, DNA damage to cells, and cancer initiation.

Beta-carotene has a number of attractive features as a potential chemopreventive agent. It is readily available at low cost and as a natural product in vegetables. Its action appears to occur, in part, in the late stage of carcinogenesis, and thus it may be effective among middle aged or older persons who have already been exposed to cancer initiating agents. Its relative lack of toxicity and simplicity of administration may make it acceptable to many asymptomatic people. Lastly, prescription of a naturally-occuring substance such as beta-carotene is likely to be better accepted than is proscription of exposure to carcinogens such as cigarette smoke.

To build on this research, the Chemoprevention Branch supports and stimulates both case-control and intervention studies. Retrospective case-control epidemiologic studies will include serum analysis to investigate the association of chemopreventive agents with reduced cancer risk. Presently funded studies include:

- High Selenium Intake and Risks of Human Cancer: This study evaluates the association of selenium with lung, breast and bowel cancer.

- Dietary Inhibitors of Colon Cancer: This case-control study will investigate the role of dietary factors including vitamins A, C, and E, beta-carotene, selenium, protease inhibitors, fats, and fibers in inhibiting cancer of the colon and rectum.

- Lung Cancer -- Prognostic Significance of Vitamin A Levels: This study will follow a large group of asbestos insulation workers who are at a very high risk of dying from lung cancer during the next five years. Serum levels of vitamin A and beta-carotene will be established in this group. The project has significance not only from the standpoint of studying the possible association of vitamin A with lung cancer, but also might serve as a predictor of risk and as a guide to the surveillance of high risk groups.

- Diet, Vitamin A, Serum Retinol, Beta-Carotene and Cancer in MRFIT: This case-control study will evaluate the relationship between dietary vitamin A and beta-carotene intake, and serum retinol and beta-carotene levels to cancer deaths of participants in the MRFIT study. Multiple dietary records collected annually on 12 thousand men over a period of seven years will be used for the dietary analysis.

Intervention studies in chemoprevention utilize compounds identified as inhibitors of the carcinogenic process. Agents include, but are not limited to, micronutrients, such as vitamin A, C, and E, and synthetic retinoids (see Table 3). Studies aimed at reducing the incidence of cancer are described below.

Chemoprevention of Bladder Cancer

This is a Phase III randomized controlled clinical trial to assess the ability of N-(4-hydroxyphenyl) retinamide (HPR) at 300 mg/day to prevent or delay recurrent bladder cancer in 500 patients with a previous history of localized, superficial (P1) bladder cancer, but who are presently without evidence of disease. Endpoints will include time to first recurrence and histopathologic stage and grade of recurrence. In addition, the effect on mortality will be assessed through the National Health Service Central Register (NHSCR). After an initial two week run-in period, patients enrolled in the study will be followed every week for the first month, once a month for the next two months, and then every three months. All patients will have a clinical examination, CT scan, cystoscopy, and blood and urine sample performed at every visit after the first three months.

TABLE 3
CHEMOPREVENTION INTERVENTION STUDIES

Target Site/ Organs	Target/Risk Group	Inhibitory Agents
Bladder	Superficial bladder cancer	4-Hydroxyphenyl retinamide (4-HPR)
Breast	Breast cancer	4-Hydroxyphenyl retinamide (4-HPR)
Cervix	Cervical dysplasia	Retinyl acetate
Cervix	Cervical dysplasia	Retinyl acetate
Colon	Familial polyposis	Vitamins C, E, and Wheat bran
Colon	Familial polyposis	13-Cis retinoic acid
Colon	Adenomatous polyps	Beta-carotene
Colon	Adenomatous polyps	Beta-carotene Vitamins C and E
Lung	Chronic smokers	Vitamin B_{12}, folic acid
Lung	Smoking males	Beta-carotene
Lung	Asbestos	Beta-carotene Retinol
Skin	Albinos	Beta-carotene
Skin	Basal Cell	Beta-carotene Vitamins C and E
Skin	Basal cell carcinoma	Beta-carotene
Skin	Actinic keratoses	13-Cis retinoic acid
Skin	Basal cell carcinoma	Retinol 13-Cis retinoic acid
All Sites	Physicians	Beta-carotene, aspirin
All Sites	Dentists	Retinyl palmitate Sodium selenite Vitamins B_6 and E

Breast Cancer Prevention with Synthetic Retinoid (HPR)

This is a Phase III clinical trial to evaluate the effectiveness of N-(4-hydroxyphenyl) retinamide (HPR) in preventing new primary lesions of the contralateral breast in women with breast cancer. About 5,000 patients treated for Stage I breast cancer, who remained with no evidence of disease and who did not receive adjuvant endocrine or chemotherapy treatment, will enter in three years. Patients will be followed-up every four months for at least seven years.

Chemoprevention of Cervical Cancer

Two separate Phase I clinical trials have determined the topical or systemic toxicities associated with escalated dosages of a topical retinoid (either trans retinoic acid or retinyl acetate) when applied to the cervix of women with mild to moderate cervical dysplasia. Two multi-institutional, randomized, placebo-controlled Phase III trials, one using retinyl acetate on a collagen sponge insert in a cervical cap delivered to the cervix and another using retinyl acetate in a topical, self-administered vaginal gel, will begin in 1984.

Chemoprevention in Polyposis

This randomized, double-blind clinical trial is assessing the effect of the combined administration of ascorbic acid and alpha tocopherol alone, or with wheat fiber, on rectal ademonas in patients with polyposis coli who have previously undergone colectomy and ileorectal anastomosis. At the present time, 1.5 years into the trial, 68 patients have been included and 61 evaluable patients are continuing on the trial. The investigator expects to perform the first interim analysis of the data in late 1984, which will be two years after the initial entry of participants.

Retinoids and Cancer Prevention in Polyposis Coli

This study has two major objectives: to reduce risk through clinical trials on a population of familial polyposis coli patients using 13-cis retinoic acid as the active agent and, concurrently, to study specific biochemical effects of retinoid treatment upon colonic polyps and skin fibroblasts. The study population has been recruited and the investigator expects to enter 40 patients into this study in 1984.

Adenomatous Colonic Polyps, A Vitamers and MFO Induction

This study will include a clinical trial using beta-carotene in subjects found to have adenomatous polyps, and a case-control study to test the hypothesis that low consumption of vitamin A compounds and/or marginal vitamin A status is associated with development of colonic adenomatous polyps and/or colonic adenocarcinoma. Recruitment for the case control and risk reduction clinical trial is in progress.

Nutritional Prevention of Polyps in the Large Bowel

This study is a randomized, double-blind placebo controlled, 2X2 factorial design clinical trial of the efficacy of nutritional supplements in preventing adenomatous polyps of the large bowel in persons at high risk for this condition. Study participants are to be assigned to one of four treatment groups: (1) beta-carotene (25 mg); (2) vitamin C (one gram) and vitamin E (alpha tocopherol 400 mg/day); (3) beta-carotene, vitamin C, and vitamin E or (4) a placebo. The study is designed to detect a 35 percent reduction in polyp incidence attributable to either beta-carotene or vitamin C and E supplementation.

Localized B_{12}: Folate Deficit and Lung Cancer in Smokers

This study proposes to address the hypothesis that components of tobacco smoke attack some forms of B_{12} and folate coenzymes rendering them inactive and that this exposure would lead to localized B_{12} and folate deficiency in bronchial epithelium in smokers. This clinical trial will provide folate and B_{12} supplementation to smokers to prevent or reverse progression of cellular changes. Recruitment of the study population has begun.

Pilot Clinical Trial of Beta-Carotene and Lung Cancer

This study is to determine the feasibility of a randomized, double-blind clinical trial to test whether increased beta-carotene as a dietary supplement will reduce the risk of lung cancer and other diseases among men aged 55 to 70 years who smoke one or more packs of cigarettes daily. Recruitment will be done in collaboration with the United Steel Workers of America and will commence in late 1984.

Beta-Carotene and Lung Cancer Chemoprevention

A high risk cohort of men, occupationally exposed to asbestos, and a selected group of hospital patients with abnormal sputum cytopathology will be entered into a randomized clinical trial of beta-carotene plus retinol versus placebo to investigate the role of these as lung cancer preventive agents. The study is to commence in 1984.

Chemoprevention of Skin Cancer in Albinos

This study is being conducted among a population of albino Africans in Tanzania to determine the chemopreventive role of beta-carotene in skin cancer. It consists of two parts: (1) an epidemiological study to document the factors which affect the occurrence of skin cancer; and (2) a double-blind clinical trial to study the efficacy of betacarotene in preventing skin cancer in this group. A demographic study and a Phase I trial have been conducted. A total of 400 albinos have been identified and will serve as the target group for the Phase III trial which will begin in late 1984.

Chemoprevention in Basal Cell Carcinoma

This study has three specific aims: (1) double-blind, randomized, placebo-controlled trial to study whether beta-carotene in combination with ascorbic acid and alpha tocopherol in patients at high risk for multiple basal cell carcinoma may reduce the occurrence of new tumor; (2) to determine the role of immunological and genetic factors in basal cell carcinoma; and (3) to evaluate the influence of these natural inhibitors on host immunity. A total of 120 patients will be enrolled beginning in 1984.

Chemoprevention Trial of Beta-Carotene in Skin Cancer

This is a randomized, double-blind, placebo-controlled clinical trial to determine the efficacy of beta-carotene as a chemopreventive agent for non-melanoma skin cancer. A total of 1,975 subjects from four centers will be enrolled. Recruitment began with a 4 month pilot phase and progressed to full scale enrollment in 1983. Approximately 650 subjects have been recruited and all centers are in full operation.

Chemoprevention of Skin Cancer by Vitamin A

This project has three major objectives: (1) to study the value of 13-cis retinoic acid in reducing the risk of skin cancer; (2) to study the safety and adverse effects of chronic pharmacological doses of vitamin A; and (3) to study the plasma concentrations in persons participating in the study. Patients with actinic keratoses are being recruited. The first patient was enrolled July 1984. Study planning and preparations for implementation include: staffing, contact with local dermatologists, plans for recruitment, enrollment and data management operations.

Chemoprevention of Skin Cancer by Retinoids

The purpose of this study is to evaluate the effectiveness of supplementary retinol and 13-cis retinoic acid in the prevention of non-melanoma skin cancer using a randomized, placebo controlled clinical trial. Eligible patients are those who have had at least eight basal cell and/or squamous cell carcinomas. A total of 246 patients is planned, with 82 in each of the three study groups. Recruitment has begun.

A Randomized Trial of Aspirin and Beta-Carotene in U.S. Physicians

This randomized, double-blind clinical trial will test the effectiveness of alternate day use of aspirin and beta-carotene in the prevention of coronary heart disease and cancer, respectively, in a population of approximately 22,000 U.S. physicians. Of the approximately 240,000 age-eligible U.S. male M.D.s who were mailed questionnaires, 33,184 physicians were eligible and willing to participate. These physicians were enrolled in a run-in phase of the trial. As of August 1984, 21,892 have been randomized with a projected total of 22,000 by the end of the randomization phase.

A Pilot Study of Vitamins and Selenium Among Dentists

This is a pilot study to determine the feasibility of a factorial trial of selenium in the form of sodium selenite, vitamin E and retinyl palmitate in the prevention of cancer and vitamin B_6 in the prevention of coronary heart disease. The baseline questionnaire has been designed and mailings to 2,000 dentists has begun.

As outlined in Table 3, the Branch now supports 18 clinical trials. All received peer review for scientific merit and a Safety and Protocol Committee review for completeness of the protocol. Additionally, each was reviewed for safety and toxicity. Each study protocol is on file in the Chemoprevention Branch office and has been submitted to the FDA and to the pharmaceutical company supplying the drug.

ACCOMPLISHMENTS

An RFA on the role of micro and macronutrients in the prevention of cancer was released in August 1983 and February 1984. A total of 53 applications was received. Several additional studies will be funded by the end of FY 84.

The cooperative agreement mechanism has been utilized successfully by the Branch to fund chemoprevention intervention trials. With this funding mechanism, an assistance relationship exists between the NCI and the investigator, where the investigator has primary responsibility for development and performance of the study, and the NCI assists in securing the drug and files the Investigational New Drug (IND) application with the FDA.

The first annual Chemoprevention Clinical Trials Workshop was held May 17-18, 1984. Approximately seventy participants were in attendance, thirty-five of whom were principal or co-principal investigators of prevention clinical trials or NCI staff intimately involved with these trials. The focus of the workshop was on the problems involved in conducting these trials and on proposing solutions. The workshop proceedings will be published in late 1984.

A total of 11 Investigational New Drug Applications (INDs) have been filed with the Food and Drug Administration. Registered under these INDs are 22 clinical chemoprevention trials. The investigational agents include: beta-carotene, retinol, retinyl acetate, 13-cis retinoic acid, ascorbic acid, alpha tocopherol, folic acid, hydroxocobalamin, vitamin B_6 and sodium selenite. Activities have also included arranging for the production, finished product formulation, packaging and shipping of investigatonal agents to the Principal Investigators and Research Institutions involved in NCI-supported human chemoprevention trials. As part of the initial IND-monitor site visits, program staff have provided advice on the plans and adequacy of facilities for investigational drug receipt and distribution, the randomization schemes and the management of data as required for IND sponsored clinical trials.

A number of RFPs and contract agreements were finalized, including:

- An RFP was finalized in the areas of in vivo efficacy evaluation in animal model systems and for the synthesis, encapsulation, and bioavailability of chemopreventive agents. Thirteen applications were received and 12 proposals were approved for issuance of a Master Agreement to fund Task Orders.
- An RFP was issued to establish an Information Resource and Data Management System for the Chemoprevention Program. Proposals have been received and have undergone review for awards.
- RFPs for in vitro and in vivo evaluation of chemopreventive agents were issued in June 1984.
- A project plan for preclinical toxicology evaluation of chemopreventive agents that are candidates for chemoprevention intervention trials was completed and an RFP is scheduled for release in 1984.
- An interagency agreement was completed with the National Bureau of Standards to establish a quality control program in clinical chemistry to increase the accuracy and precision of determinations for vitamins and trace elements in sera and other biological materials.
- The contract for Phase I trials in new chemopreventive agents was awarded in the fall of 1984.

PLANS

A concept for chemoprevention trials in selected cancer sites was approved by the Board of Scientific Counselors in May 1984. A subsequent RFA will call for applications in chemoprevention clinical trials, specifically related to head and neck, breast, bladder and colon cancer.

A study of the chemoprevention of skin cancer in albinos is continuing. This project, conducted in a population of albino Africans in Tanzania, is a study of chemoprevention of skin cancer using carotenoids.

A study of the chemoprevention of cervical cancer is continuing. A Phase I study has been successfully completed. A Phase III study to evaluate whether topical retinoids will reverse mild to moderate cervical dysplasia and prevent the development of cervical cancer is being implemented.

Intervention trials for prevention of breast and bladder cancer will be implemented with 4-hydroxyphenyl retinamide (HPR). In animal models, this compound has been shown to be the most active and least toxic synthetic retinoid presently available.

The quality control in clinical chemistry program, which has been implemented, will assist investigators in evaluating the clinical chemistry aspects of ongoing and planned clinical studies supported by DCPC.

An information resource and data management system for the chemoprevention program will be established. Summary evaluation of at least 100 potential chemopreventive agents concerning factors such as efficacy, toxicity, availability and cost will be completed and the criteria for priority selection for clinical trials will be reviewed. Monographs will be prepared on the most promising agents.

An *in vitro* and *in vivo* screening program to identify new or potential chemopreventive agents will be initiated.

Preclinical studies of the toxicology of chemopreventive agents are being implemented to evaluate the acute, subacute/subchronic and chronic toxicity of chemopreventive agents. These studies will be performed in animals and will include conventional short term studies, life-time studies in rodents, and multigeneration teratogenicity studies.

Phase I human clinical trials to evaluate toxicity and safety of agents under consideration as potential human chemopreventive agents are being implemented.

A workshop to consider the potential use of interferon in the prevention of cervical dysplasia was held in 1984. Since there is growing evidence that cervical dysplasia may be associated with human papilloma virus infection, the use of interferon to reduce or eliminate cervical dysplasia will be considered.

STAFF

Chief: Winfred Malone, Ph.D., M.P.H.

Program Director: Gary Kelloff, M.D.
Mary Ann Sestili, Ph.D.

Senior Investigator: Charles Boone, M.D., Ph.D.
Donald Buell, M.D.

Program Analyst: John G. Dell, M.P.A.

Secretarial Support: Judith Binstock
Sharon Hughes

Diet and Cancer Branch

OBJECTIVES

The Diet and Cancer Branch (DCB) has the lead responsibility within the Prevention Program for encouraging and supporting research on the role of diet and nutrition in cancer control. The primary goal of the Branch's programs is the reduction of cancer incidence through dietary modification. In view of the existing gaps in our knowledge regarding the type of dietary modification to reduce cancer incidence, the Diet and Cancer Branch is organized to:

- Develop, plan, direct, and coordinate a research program in diet, nutrition, and cancer as it relates to cancer prevention;
- Develop, refine, and test hypotheses of diet and the etiology and prevention of cancer;
- Develop quantitative methods to monitor nutritional intake in large populations and to facilitate accurate conversion of diet into nutrient content;
- Study baseline dietary data on populations participating in controlled clinical trials, assess strategies for altering diet in relation to cancer risks, weigh scientific knowledge and the impact of such strategies, and conduct applied research on dietary modification and cancer;
- Oversee diet, nutrition, and cancer activities, coordinating these with related activities in other divisions of the NCI, other NIH institutes, and other research and health agencies.

The specific objectives for immediate implementation relate to the first three cancer control research phases: hypothesis testing, methods development, and controlled clinical trials. With the newly planned projects, the Branch will seek to:

- Identify areas for applied and basic research on specific dietary factors that serve as inhibitors or promoters of carcinogenesis;
- Develop and refine dietary and nutritional assessment methodologies, including refining of nutrient data banks, to permit reliable and valid measurement of specific dietary factors;
- Develop methods for enabling desirable changes in eating behavior and for measuring such changes;
- Provide, through support of risk reduction clinical trials, scientifically-based information on the preventive role of dietary factors in cancer formation and prevention.

OVERVIEW

In support of its goals and objectives, the Diet and Cancer Branch will support extramural studies to address knowledge gaps regarding the type of dietary modification required to reduce the incidence of, and improve patient survival from cancer.

This includes studies to assess and measure dietary factors in the context of human intervention trials to:

- Determine if primary prevention is possible through food selection and/or food supplementation;

- Identify the role of dietary substances in cancer prevention, including: nutrients and food groups (e.g., fats, vegetables), minerals and trace elements, non-nutrient food substances (e.g., fiber), vitamins, and interactions of nutritional factors;

- Evaluate dietary and nutritional approaches to prevention, including possible modifiers of host resistance to the development of neoplasms;

- Develop and test methods, including biological indicators, to monitor, assess, and validate nutrient intake with specific relevance to clinical trials in cancer prevention;

- Develop and test methods to quantify specific components of the food supply with preventive potential with specific relevance to clinical trials in cancer prevention.

Studies of toxicity conducted in the context of large-scale human intervention research:

- Examine the long-term toxicity of dosing with various dietary and nutritional interventions in animal models as a precursor to human studies,

- Determine dose-response relationships and test for acute and chronic toxicity of dietary and nutrient interventions in human populations,

- Assess the benefit/risk ratio of dietary and nutritional interventions.

Clinical trials conducted in defined populations to test for efficacy in inhibiting the onset or progression of neoplastic changes include:

- Primary prevention of cancer onset in high risk populations and/or,

- Clinical trials on populations with preneoplastic changes.

ACCOMPLISHMENTS

Nutrient Data System for International Use

The Diet and Cancer Branch, DCPC is supporting the development of an International Food Composition Data System (INFOODS). This is in response to the need for more complete, reliable and comprehensive information on the nutrient and non-nutrient composition of foods, beverages and their ingredients.

The current interest in the area of nutrition, diet and cancer has called attention to some major deficiencies in the data base available to support a variety of research activities in the field. This has been especially evident in epidemiologic studies where attempts are being made to characterize the dietary differences existing among various populations which have markedly different incidences of chronic diseases, including cancers thought to be associated with diet. Such studies have been able to characterize international differences in diet by broad, nutrient-food categorizations, but suffer from a dearth of detailed information on the nutrient content of the enormous variety of foodstuffs consumed by different populations, and by the subgroup populations within each of the countries or geographic areas.

At the present time, there is no internationally agreed upon food composition data system that provides a continuum of information on food composition. Current diet and disease studies require data on the human requirements or allowances for essential nutrients and quantified data on the ability of the food supply to provide these factors. In addition, information on other chemical components of foods that represent protection for or risk to good health is needed. Such a comprehensive data base would be helpful in providing criteria for formulation of public policy on diet-related public health issues.

Efficient forms of gathering and processing data are now available. Modern computer and telecommunication offer many advantages over the traditional forms of data sources such as handbooks and journals.
Such advantages include:

- Easier updating,
- Expanded search strategies,
- Multiple computations can be performed without need of human interpretation,
- Rigorous and uniform rules for acceptance of data results in data base of known quality,
- Costs are likely to be more advantageous.

The INFOODS project will provide better data to interpret epidemiological studies and dietary intake data to draw conclusions about individual food substances and their relationship to disease. The National Heart, Lung and Blood Institute, Food and Drug Administration and U.S. Department of Agriculture, have joined the initiative by promising financial and technical support. A contract to perform the development of INFOODS was funded in FY 84.

A paper entitled, "Considerations in Designing a System for Description of Food and Flexible Retrieval of Relevant Data," was presented by the Acting Chief of the Diet and Cancer Branch at the 9th International Conference of the Committee on Data for Science and Technology.

Risk Reduction Clinical Trials for Breast Cancer

Epidemiological studies have repeatedly shown an association between dietary fat and the occurrence of cancer at several sites, particularly the breast. Numerous experiments on animals also indicate that dietary lipid influences tumorigenesis in the breast. A high fat diet (about 40 percent of the total calories) is common in practically all developed countries, except in Japan, which exhibits a lower incidence of breast cancer compared to the other developed countries.

Based on strong evidence that lowering the percentage of calories from dietary fat will reduce the breast cancer incidence, the Diet and Cancer Branch has initiated two clinical trials; one will test the impact of a low-fat diet intervention in women who are at high risk for breast cancer, the other will test the impact of the same intervention on women with Stage II breast cancer.

The multi-institutional randomized clincial trial of a low fat diet (15 percent of calories) in Stage II breast cancer was initiated in July 1984, involving eight Clinical Units, a Nutrition Coordinating Unit, and a Statistical Coordinating Unit, all funded through the cooperative agreement mechanism. This trial, using a single protocol, is being initiated in three stages. The first stage involved a meeting between the investigators and the NCI staff in July 1984, for development of the protocol. The second stage involves implementing the protocol with particular emphasis on documenting protocol adherence in the study and control groups. The third stage will be a full-scale clinical trial with approximately 2,000 patients participating in a four-year study.

A similar multi-institutional randomized clinical trial is being initiated with participation of approximately 6,000 subjects who are considered to be at high risk of developing breast cancer. Forty-three applications were received in response to an RFA and were reviewed in July 1984. Awards were made in September 1984, followed by the protocol development and feasibility stages of this study.

Modification of Dietary Behavior

Diet modifications, such as dietary fat reduction and increased fiber intake, appear to play a role in prevention of cancers in several sites, particularly, the breast and colon. The NCI is preparing to develop large-scale intervention trials in order to test hypotheses related to diet modifications.

To conduct such studies, however, methods of altering eating behavior in large human populations are needed. While it is clear that people do markedly alter their diets during the course of their lives, little information is known about the factors responsible for such changes. Long-term research on patterns of food selection by humans and the factors that affect them is lacking. Thus, even when knowledge about diet and disease relationships justifies dietary interventions, no proven measures exist to help people to modify their long-term food intake. The Diet and Cancer Branch is, therefore, initiating interdisciplinary behavioral and nutritional investigations to develop and test methods of altering dietary behavior relevant to cancer control within populations at high risk for colon and breast cancer.

Dietary Fiber

A number of epidemiologic studies suggest that diets with a high intake of total fat and a low intake of dietary fiber and certain vegetables are associated with an increased incidence of large bowel cancer in humans. Only limited amounts of data on the quantity of total dietary fiber and individual fiber fractions such as cellulose, hemicellulose, lignin, and pectins are available for most foods. The limitations of these analytical data seriously impede the elucidation of the significance of these dietary components to the incidence of cancer. Two contracts have been awarded for developing new methods for the determination of total dietary fiber and fiber fractions in foods, and for applying these methods to determine the fiber content of those foods which contribute a major portion of dietary fiber in the U.S. These contracts are expected to result in a reliable data base on total dietary fiber and fiber fractions which are needed for the dietary assessment and prevention studies of the NCI.

As a complement to this project on the analytical data on dietary fiber, a concept was recently developed by DCB staff and approved by the Board of Scientific Counselors for funding three studies on the physiochemical effects of fiber in humans, in order to elucidate the possible protective role of the various fiber components in carcinogenesis, and to develop dose-response data on these fiber components in humans. These studies are a prelude for intervention studies involving dietary fiber.

Retinoids and Carotenoids

Dietary intake of vitamin A and its precursors, the carotenoids, appears to be inversely related to the incidence of carcinoma at several sites. Numerous studies have associated a reduced incidence of cancer with a high intake of certain vegetables, suggesting that the known vitamin A active carotenoids may be responsible for this effect. Much of the epidemiologic data do not, however, distinguish between the effects due to vitamin A or carotenoids. The difficulty in separating the effects stems in part from the lack of analytical data of these components in foods. A plan to fund a contract analyzing the various retinoids and carotenoids in food should result in a reliable database of retinoids and carotenoids in the U.S. food supply. The data will be used in both retrospective and prospective epidemiology studies and in case-control and intervention studies. As a complement to these studies of food composition of vitamin A and carotenoids, studies on human metabolism and physiology of retinoids and carotenoids will be supported. These grants will be funded in early 1985 to increase an understanding of the metabolism of these substances in the human gastrointestinal tract, their uptake and regulation by the liver and kidney, their concentration in organs and tissues, and the homeostatic mechanisms which control blood levels of retinoids and carotenoids. These projects will aid in the dietary recommendations for reduction of specific cancers for the year 2000.

Workshops

A workshop entitled Dietary Fiber and Cancer was held in April 1984. The objectives of the workshop were to bring together reseachers in the area of dietary fiber and cancer to review progress in this area and offer suggestions for future research needs. Talks focused on epidemiology of colon cancer, experimental animal models, and the protective role of fiber in diets.

A workshop on the Health Habits and History Questionnaire was held in June 1984 to obtain a critical review of the dietary frequency questionnaire developed by DCPC before utilization in NCI studies.

A workshop with representatives from three Latin American countries, Chile, Costa Rica, and Venezuela, in collaboration with the Pan American Health Organization, was held in September 1984. The workshop discussed the high incidence of stomach cancer in these countries, as well as current dietary survey data in order to formulate plans for future dietary intervention studies.

PLANS

Five concepts were reviewed and approved by the Board of Scientific Counselors in FY 84. These concepts include: Methodology and Analysis of Fiber in Foods, Physiochemical Effects of Dietary Fiber, Methodology and Analysis of Retinoids and Carotenoids, Human Metabolism and Physiology of Retinoids and Carotenoids, and Modification of Eating Behavior and Cancer Prevention. The twelve projects proposed in these concepts will be funded in FY 85. Three other projects planned by the Branch are described below.

Stomach Cancer Intervention Trials

A pilot study will be conducted in selected Latin American countries to investigate the relationship of intakes of certain nutrients and non-nutrients such as nitrates, selenium and vitamin C, and the high rates of stomach cancer. Subsequently, a dietary intervention study will be conducted to test the possible relationship between dietary factors and stomach cancer.

Large-Scale Dietary Intervention

Plans are being formulated for a large-scale community dietary intervention project in Stockholm County, Sweden. Dietary intervention for this county of approximately 1.5 million people will focus on reduction of dietary fat, and the increase of dietary fiber, selenium, and vitamins A and C by selection of specific types of foods and food products.

Provisional Food Table For Dietary Assessment

This will be a collaboration between the NCI and the USDA, to establish provisional reference data bases on carotenoids, dietary fiber, and fiber components in foods. The NCI needs these data bases for its intervention studies and for calculating dietary intake in clinical trials.

STAFF

Acting Chief:	Ritva R. Butrum, Ph.D.
Senior Investigator:	Carolyn Clifford, Ph.D. Elaine Lanza, Ph.D.

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Occupational Cancer Branch

OBJECTIVES

The Occupational Cancer Branch (OCB) has the primary responsibility within the Prevention Program to encourage and support research in cancer prevention and control in target populations who are at high risk of developing cancer due to occupational exposures. The primary goal of the Branch's program is the reduction of cancer through the identification, evaluation, and application of available cancer control strategies. The Branch supports prevention studies to develop strategies and methodologies whose impact will be measurable in terms of reduced morbidity and mortality among high-risk occupational populations. Based on known occupational carcinogens, worker population characteristics and the worksite, the Occupational Cancer Branch is pursuing the following objectives:

- To compile clinical, laboratory and epidemiologic data on work-related carcinogenic agents;
- To identify, characterize, and register selected occupational populations at high risk of cancer;
- To assess medical surveillance systems and to develop and evaluate new approaches to surveillance of high-risk populations;
- To conduct research for effective cancer prevention and control methods;
- To demonstrate the feasibility of disseminating information on effective intervention procedures.

OVERVIEW

The Occupational Cancer Branch promotes the philosophy and principles of cancer control sciences to the field of occupational health and to the occupational medicine community. The Branch encourages and supports extramural studies in the areas of worksite epidemiology, cancer control and prevention methodologies, medical surveillance strategies, and innovative methods of disseminating proven preventive techniques for worker protection. The Branch collaborates with other Federal agencies such as the National Institute of Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) through Interagency Agreements, and with professional organizations such as the American Association of Occupational Health Nurses.

One area of investigation is studies to identify, register and characterize high-risk occupational populations. First, high-risk populations are being surveyed for the purpose of identifying potential populations for the application of cancer control measures. Second, hazard evaluations are being conducted within the workplace to identify suspicious chemicals and populations who are at risk from them. Third, a strategy is being developed to register high-risk groups for future interventions and surveillance.

A second area is studies to determine effective cancer prevention and control methodologies. The Branch continues to build on its past experience in cancer control through the education of workers and health personnel within the worksite. These programs utilize existing knowledge, while continuing to develop more effective educational approaches, which can supplement or replace those already in use. For example, the worker protection educational programs sponsored under an NCI-OSHA Interagency Agreement, were examined for strengths and weaknesses. These programs have been superseded by a grant program which is targeted toward specific carcinogen exposures and defined worker populations. An evaluation protocol has been carefully designed for the purpose of measuring the effectiveness of the educational efforts. The Branch is also conscious of the limitations which measure the impact of educational efforts on morbidity and mortality. The Branch is, therefore, interested in collaborating with other Branches in studies designed to develop and test new prevention and detection approaches yielding quantitative results. These studies will provide data on the following cancer sites: lung, bladder, and colorectal.

OCB also promotes studies of medical surveillance systems and strategies. The Branch is interested in testing various systems and strategies for monitoring large occupational populations, and high-risk populations. These studies include the examination of the effectiveness of various organizational and administrative frameworks for surveillance, such as community-based approaches, hospitalbased, worksite based or others. The Branch is concerned with the nature and validity of screening modalities used within surveillance systems, laboratory resources, available facilities, and methods of data collection, analysis, and recording. In addition, the Branch is examining the feasibility of establishing a network of universities with research units of proven competence and experience in occupational cancer research. Collaborative efforts are expected to overcome some of the barriers inherent in the study of high-risk occupational cohorts (e.g., small cohort sizes in any single location). This "pooling" of research expertise on high-risk worker populations is expected to facilitate epidemiological studies on cancer of the sites associated most frequently with occupational carcinogens (see Occupational Cancer Research Network, later in this section).

A further area of investigation is studies to demonstrate the feasibility of disseminating information about effective intervention procedures and approaches. The Branch is interested in achieving broad dissemination of relevant information through publication of its research results in medical, scientific, and public health journals and in selected media for the public. The Branch is currently pursuing activities concerned with the dissemination of cancer control and prevention information within the workplace, which will help workers reduce or eliminate exposure to carcinogens. Additionally, the Branch is currently supporting studies undertaken by labor organization grantees (see Cancer Control Studies in Occupational Settings below). Lastly, the Branch is active in identifying those health professional, management and worker groups within the worksite who are relevant to worker protection programs. Among health professionals, the Branch has developed an ongoing program of cooperation with the National Association of Occupational Health Nurses. The occupational health nurse is acknowledged as having the most direct contact with workers. These health professionals enjoy worker confidence and are in an excellent position to become aware of cancer problems, since worker complaints and symptoms are initially brought to their attention. However, there are serious knowledge gaps regarding the performance of nurses in the worksite in regard to cancer prevention. This knowledge gap was addressed in a workshop during which participants discussed worksite strengths and weaknesses. Recommendations were made to the Branch which included the identification of more effective worksite cancer prevention activities and the recognition of a need for greater nurse participation in worker education.

ACCOMPLISHMENTS

The Branch has vigorously pursued its activities during the past year. Branch objectives have been refined and expanded in response to advice and counsel from advisory groups and staff. Additionally, the Branch has drawn upon the expertise and cooperation of Federal agencies which are mandated by law, to concentrate efforts on the work environment. Through Interagency Agreements and informal interrelationships, the Branch has successfully engaged in activities ranging from ongoing communications leading to the exchange of information and ideas to jointly designed and implemented studies.

Through its many cooperative activities with organizations, whose membership includes key workplace health professionals, a firm base of understanding and purpose has been established which is being translated into specific joint endeavors. Steady progress is being made by five labor organization grantees who are measuring the impact of worker education programs on worker cancer control behavior and in changes in the organization and administration of the work environment. In less than a year of performance, education/evaluation models have been developed which will be subjected to careful evaluation protocols to determine their individual success and the applicability of the intervention designs. The Branch has successfully called upon educational institutions and other relevant organizations to pool resources and talents into a network arrangement to engage in occupational cancer studies. More detailed descriptions of individual program areas follow.

Cancer Control Studies in Occupational Settings

This education/evaluation program seeks to: (1) measure the impact of prevention education on workplace behavior change; and (2) develop a greater understanding of those workplace organizational, administrative, and social factors which serve as reinforcements or deterrents to the cancer control goals of education interventions. These evaluation studies are being undertaken to develop information on effective cancer control approaches and methods to reduce or eliminate exposures to cancer hazards which can be applied to other occupational settings. The five grantees funded under this RFA are labor organizations.

- Painter Cancer-Risk Reduction Evaluation -- International Brotherhood of Painters and Allied Trades: This grantee is collaborating with the School of Public Health at Harvard University to conduct a study of cancer control in high-risk painters exposed to heavy solvents. The study involves training in exposure-reduction and will assess the utility of a neurotoxic screening questionnaire which measures the reduction in exposure.

- Occupational Cancer Control Comparison of Two Educational Models -- The International Union, United Automobile Workers of America: This grantee is comparing the effectiveness of two educational strategies aimed at motivating workers to recognize and reduce exposure to carcinogens in automobile assembly plants. Onehalf of the study plants will receive an established UAW educational program with basic information on carcinogen recognition and control. The other half will receive additional structured educational material in small groups, with follow-up over an 18-month period.

- Cancer Prevention Education for Coke Oven Worker -- The United Steel Workers of America: The United Steel Workers of America, in cooperation with the University of Pittsburgh, is conducting a study to reduce exposure to coke oven emissions in steel plants. The study provides a training program to individual workers and local union safety and health representatives. Comparison populations will include nonparticipants at the test site.

- Cancer Control Studies in the Rubber Industry -- The United Rubber, Cork, Linoleum and Plastic Workers of America: In collaboration with the University of North Carolina at Chapel Hill, the United Rubber, Cork, Linoleum and Plastic Workers of America will conduct a study to alter worker behavior to reduce exposures to cancer risks in rubber manufacturing plants. The overall evaluation design is a randomized educational intervention trial. Plants, stratified by composition of the work force and level of hazardous material used in the manufacturing process, will be randomly assigned to control and experimental groups. The experimental group will receive an educational program based on the health belief model, identifying critical factors associated with behavioral change. The control group will receive the standard educational program. Behavior change in both the experimental and control groups will be measured by various indicators specified in the evaluation model.

- Cancer Control Educational Evaluation -- The International Chemical Workers Union: This grantee, in collaboration with the University of California at Los Angeles, is conducting a nationwide field experiment to evaluate the effectiveness of an education intervention program to reduce carcinogen exposures in chemical manufacturing plants. The project involves both process and outcome evaluation, with a heavy emphasis on behavioral, organizational, industrial hygiene, and medical monitoring measures obtained from questionnaires, plant tours, and ICWU records.

Occupational Cancer Research Network

The Occupational Cancer Research Network is made up of universities and other institutions qualified in occupational cancer research who will conduct medical surveillance and interventions in high-risk occupational populations. A collaborative arrangement between diverse research units, which are geographically distributed, is expected to help overcome certain characteristics of occupational cohorts, such as small sample sizes. The initial task of this network is to develop standardized procedures, protocols, and forms for performing the medical examination and obtaining the occupational and medical histories. Standardized methods for data collection and analysis is the first step in the establishment of cooperative studies.

This project involves three types of studies. The first, initial studies, provides for identification of potential study populations. Generally, this involves the identification of high cancer-risk groups. Information to be collected includes the following: (1) target worksites and cancer sites being investigated; (2) estimated incidence/ mortality of cancer in proposed populations; (3) estimated size and age distribution of study population; and (4) duration of employment exposure.

The second type of studies has three components. The first component is development of an experimental design for the intervention study. Information to be obtained includes the following: (1) characteristics of intervention procedure; (2) known risk factors for study populations; and (3) statistical considerations such as power calculation. The second component is registration of potential study populations. This involves identifying, locating, and contacting individuals in the population. The third component is the baseline medical examination of the study population which includes special procedures for assessing the status of the target tissue in this population. Occupational and medical histories will be obtained.

The third type of studies involves randomized controlled trials of interventions (Phase III) which include newer detection methods, hazard reduction and chemoprevention. The initial study populations to be examined will include population at high risk from exposures to asbestos and carcinogenic aromatic amines.

Hazard Evaluation Activities

An Interagency Agreement has been signed between the NCI and the NIOSH for studies which will identify populations at high cancer-risk due to occupational exposures. A list of candidate populations for hazard evaluation has been reviewed and priority areas have been defined. Regular reporting of progress is underway. Priority cancer sites under consideration for study include: lung cancer diagnosed in welders without a confounding exposure to asbestos, bladder cancer in workers exposed to aromatic amines, skin and lung cancer diagnosed in roofers, and gastrointestinal cancer found among metal machinists.

Medical Surveillance System Research

The goal of this grant program is to develop a community-based model of surveillance for cohorts of worker who are at increased risk of cancer due to past workplace exposure to carcinogenic agents. The study addresses such issues as community organization and planning, identification of resources, collection of screening data, notification of workers, interpretation of test findings, and data collection and analysis. A critical measure of success, which is being achieved, is the development of community based support for surveillance systems.

PLANS

In FY 85, the Branch will continue to develop cancer prevention activities aimed at further reductions in occupational cancer incidence, morbidity, and mortality. The Branch will continue to support and promote worker education research activities, develop medical surveillance systems demonstrations, increase the networking of specialized resources in occupational cancer research, and promote cooperative prevention efforts with relevant health professionals. These activities should, over time, result in more enlightened management, more effective workplace health professionals, better educated worker populations, and increased participation in studies aimed at improving cancer control in the workplace. Current studies should give new meaning to the design of medical surveillance programs for worker populations, and should result in the availability of increased data on the carcinogenicity of chemicals in the workplace and on those populations at risk.

The Branch will expand its activities by forming cooperative arrangements with other branches in the Prevention Program to support research in: the use of chemopreventive agents in worker populations, the impact of various dietary regimens in the control of occupational cancer, and the application of new detection techniques to identify individuals at high risk for cancer. In FY 85, the Branch will conduct activities in the following areas.

Systems Monitoring of Cancer in Occupational Populations

The Branch will explore the feasibility of a SEER-like occupationally based surveillance system for cancer incidence, mortality, and morbidity. This activity will track cancer in large occupationally based populations and monitor any significant increases or decreases in cancer rates. It is envisioned that exposure data on toxic substances could be linked to this system so that the effects of toxic agents can be also monitored.

Worker Education -- The Notification Process

Worker notification has not been sufficiently studied as an education tool. Studies are needed to develop effective strategies for notifying workers about the risks of carcinogenic exposure and the available control measures to minimize risk. Worker compliance and behavior changes will require effective communication to motivate the worker to take action. Such notification must be delivered by individuals who are cognizant of the ethical, moral and regulatory aspects of the notification process and in whom the worker has confidence and trust. Support mechanisms must be developed to assist the informed worker. Worker notification will be explored in terms of its positive influence on reduction of exposure and on the increased utilization of surveillance programs which could have an impact on cancer incidence and mortality.

Worker Education -- Health Protection

Research indicates that there is a strong relationship between worker lifestyle and the incidence of cancer. Perhaps the most widely recognized relationship is the increased risk of cancer among those individuals who smoke and are exposed to carcinogens, such as asbestos. There is also sufficient evidence to warrant the support of studies of the relationship between diet and nutrition and the development of polyps and colorectal cancer among workers. Additionally, the impact of high alcohol consumption, while recognized in larynx and oral cavity cancers, has not been widely studied in its relationships to occupational cancers, such as urinary bladder and colon cancer. Profiles of worker populations indicate a worker lifestyle that includes: smoking, ingestion of high fat, high caloric diets, and consumption of alcoholic beverages. There is, therefore, a need for research among occupational cohorts to address the changes in lifestyle which may reduce cancer incidence toward achieving the year 2000 goal.

Public Education -- Medical Surveillance Systems Demonstrations

Research indicates that the exposed workers' family and community must be educated about worksite cancer risk so that they may support immediate and long range surveillance systems for high-risk exposed workers. Public education is traditionally conducted through mass media campaigns (i.e., television, radio and press) and publications (e.g., brochures, pamphlets and leaflets). The solicitation of public support and involvement in surveillance system is a unique situation, still largely unexplored, and many approaches will need to be tried. Circumstances may warrant the sponsorship of public forums, where expert presentations are followed by audience response and discussion. Research is needed to develop model public education programs which can encourage community support in resolving occupationally induced problems. A question of prime importance is how effective community planned and implemented programs are in contrast to nationally initiated and directed programs.

Professional Education

The Branch has given impetus to a program of education and involvement of worksite health professionals in worker cancer prevention programs. The initial step in this program is directed toward occupational health nurses. Among health professionals in the workplace, this profession warrants considerable attention from the viewpoint of cancer control. Although occupational nurses are members of the management team, they enjoy more worker confidence and trust than that of most management personnel. The following are planned activities.

- A study will examine the functions of occupational nurses within workplaces where employees have a high risk of exposure to known or suspected carcinogens. This will involve a national survey utilizing a questionnaire followed by direct observation of stratified sub-samples of worksites. A critical element of this survey will be an inquiry into the present cancer prevention activities of the nurses, and the potential which exists for such activities.

- Through national and regional workshops, model educational programs in cancer prevention will be developed for occupational health nurses employed in workplaces receiving no on-site physician support. Materials for the workshops will include prevention education curriculum and other educational materials developed under grants and contracts supported in the past by this Division.

- Staff will explore the possibilities of developing models of occupational prevention education/evaluation programs initiated and implemented by nurses. These studies will address workplace environments where exposures to known or suspected carcinogens exist; workplace administrative, organizational and structural elements conducive to, and supportive of, onsite prevention education programs; appropriate credentials for nurse personnel; physician support and involvement, and educational program content.

STAFF

Acting Chief: Veronica L. Conley, Ph.D.

Senior Investigator: Kenneth C. Chu, Ph.D.

Data Analyst: Gail A. Sheridan

Secretarial Support: Janice L. Holliman
Judith D. Musgrave

Cancer Prevention Studies Branch

OBJECTIVES

The major objective of the Cancer Prevention Studies Branch (CPSB) is to contribute to the cancer control process by conducting Phase III intervention studies. These trials serve the dual purposes of confirming hypotheses about cancer etiology and effecting control. Accomplishing this objective requires: (1) the pursuit of etiologic studies to generate hypotheses and to help them mature to the point that interventions are appropriate; and (2) supporting preliminary studies and ancillary research efforts that establish the feasibility of doing such interventions.

OVERVIEW

The Cancer Prevention Studies Branch conducts intramural research in the areas of diet, nutrition and cancer, cancer chemoprevention, occupational cancer studies, and other cancer prevention strategies aimed at lowering human cancer risk. This specifically involves the following.

- Nutritional and chemoprevention interventions and trials designed to test the effect of nutritional and chemopreventive agents in reducing cancer risk are planned, developed, and conducted. Safety and toxicity studies, as well as clinical studies, examining the relationships of substances under investigation to biochemical and physiological parameters are included.
- Methodologies for ascertaining study priorities and for ensuring quality control and excellence in the performance of the studies and appropriate standardization between studies are developed.
- Data systems and other resources necessary for conducting these studies are developed, coordinated, and maintained.

ACCOMPLISHMENTS

The Branch has initiated five intramural projects. They represent collaborative efforts in investigating diet and nutritional factors relating to cancer prevention; all but one involves actions or interventions aimed at lowering cancer risk; one study develops a data system which can be used to conduct further studies. The following is a brief summary of these five intramural projects, all of which will continue through FY 84.

Nutrition Intervention Study in Esophageal Cancer in Linxian, China
(Z01 CN 00112 CPSB)

The purpose of this project is to conduct two intervention trials using multiple vitamin-mineral supplements to evaluate the relation between such supplements and esophageal cancer mortality. One trial will be conducted in patients diagnosed with esophageal dysplasia (n = 2,400) and the other in the general population (n = 28,000). The studies will evaluate the effect of these supplements on regression/progression of esophageal dysplasia and total cancer incidence, total cancer mortality, and total mortality. These two studies are being conducted in Linxian (Henan Province) in the People's Republic of China (PRC). Linxian, a rural county with population of 800,000, was selected because it has the highest rate of esophageal cancer in the world, and because there is suspicion that the population's chronic deficiencies of multiple nutrients may be etiologically involved.

This study is being conducted jointly by the Environmental Epidemiology Branch of the Division of Cancer Etiology and the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control at the NCI in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences.

U.S.-Finland Epidemiologic Studies of Nutrition and Cancer (Z01 CN 00100 CPSB)

The important relationship of diet and nutrition in the development of cancer has become well known through various research efforts. Laboratory studies have shown cancer inhibitory functions for various natural and synthetic nutrients in various models, which have been corroborated by human epidemiologic studies of nutrient intake, tissue levels and cancer incidence. Vitamin A, beta-carotene and selenium have been strongly implicated for their cancer preventive potential, with evidence for the former two substances warranting clinical trials of their efficacy. In addition, the roles of other nutrients in cancer cause and prevention (e.g., dietary fats and fiber) require further investigation.

The objectives of this cooperative project with the government of Finland are: (1) to determine if either beta-carotene or alpha-tocopherol supplementation is effective in preventing lung cancer in smokers; (2) to better assess the role of selenium, vitamins A, E, and C, and fats in breast cancer development; (3) to evaluate the roles of various levels of nutrient intake to subsequent cancer.

The project includes three studies, all taking place in Finland. The first, a beta-carotene, alpha-tocopherol intervention trial in lung cancer, is a 5-year, double-blind, placebo-controlled, 2x2 factorial randomized trial of daily beta-carotene (20 mg orally) or alpha tocopherol (50 mg orally) among cigarette smokers. Any reduction of lung cancer incidence in the active treatment groups will be measured. The second is a breast cancer case-control study of selenium, vitamins A, E, C, fats and other nutrients (both serum levels and dietary history), using both benign breast disease and neighborhood controls. The importance of these nutrients in breast cancer development will be assessed. Finally, the dietary survey study will use previously collected dietary history information for a subgroup having developed cancer out of an original population cohort. Associations between various dietary components and different cancers will be assessed. The pilot clinical trial and breast cancer studies will begin September 1984.

Human Studies of Diet and Nutrition (Z01 CN 00101 CPSB)

The role of specific dietary factors in cancer prevention has been assessed through epidemiologic studies and animal experiments. For many of these agents, information is incomplete concerning their quality and form in the food supply, bioavailability, biochemical effects, and the interaction with other nutrients. To further define these parameters in the human population, a cooperative research effort between the Beltsville Human Nutrition Research Center (BHNRC), U.S. Department of Agriculture, and the Cancer Prevention Studies Branch, DCPC, is being conducted. The three year interagency agreement will encompass the development of analytical methods for routine analysis of nutrients, as well as further investigation of the pharmacodynamics and interactions of those dietary factors identified as possible cancer preventive agents.

The overall goal is to obtain further information on those factors identified as potential cancer preventive agents with respect to their quantity and bioavailability in the food supply, health effects of supplementation, and their pharmacokinetics in a healthy population, as well as improving methods for analysis of these nutrients. Investigations of the trace element selenium (Se) were conducted during the first year. Few supplemental studies have been done and many questions concerning the pharmacokinetics and bioavailability of Se in its organic and inorganic forms remain unanswered. The initial phase of the Se studies examines the pharmacokinetics of a single oral dose of selenite and selenomethionine in a healthy population having adequate Se intake at baseline. The second phase will examine the bioavailability and health effects of multiple doses of inorganic and organic selenium. Following these, a study will be conducted correlating dietary intake of beta-carotene with beta-carotene levels, retinol and retinol-binding protein levels in the blood.

Phase I Studies of Oral Synthetic Retinoids -- 4-HPR (Z01 CN 00102 CPSB)

Phase I studies are needed to provide the parameters and characteristics of acute human toxicity, establish a maximally tolerated dose, delineate basic pharmacokinetics, and indicate a starting clinical dose for the investigational drug being developed.

Vitamin A and its synthetic analogs, collectively known as retinoids, have been actively studied in relation to their requirements in normal physiology and health, as well as for their potential in prevention of human disease, notably cancer. In this regard, it has been established that: (1) supplementation with retinoids can reverse tissue metaplasia and neoplasia in various laboratory models, restoring normal cell differentiation; and (2) retinoids administered to animals can prevent chemical and viral induced carcinogenesis. They have been repeatedly shown to delay the appearance, retard the growth, cause the regression and prevent metastases of selected tumors. In addition, several epidemiological studies have shown an association of low levels of vitamin A with increased risk of cancer.

Based on this evidence and case reports demonstrating successful chemoprevention of basal cell carcinoma with large doses of the retinoid isotretinoin, a Phase I intramural clinical trial of a promising new oral synthetic retinoid, 4-HPR (N-[4-hydroxyphenyl] retinamide), has been implemented. This study has the following objectives:

- Delineate acute human toxicity patterns of orally administered 4-HPR,
- Determine a maximum tolerated/feasible dose (MT/FD),
- Evaluate the subacute toxicity of the MT/FD for 3 months,
- Observe evidence of any therapeutic effect on specific cutaneous diseases and disorders of keratinization.

The study population will include 27 dermatology patients, with qualifying skin conditions, who meet strict eligibility criteria. Dose escalation follows a modified Fibonacci search method and proceeds until the MT/FD is established. The MT/FD serves as the dose for the 3 month subacute toxicity study and will be used as the starting clinical dose for future Phase III studies in cancer chemoprevention.

Use of Isotretinoin in Prevention of Basal Cell Carcinoma (Z01 CN 00103 CPSB)

The study is a 5-year randomized double-blind clinical trial designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinomas in a high risk population, and to examine possible side effects associated with long term administration of low doses of isotretinoin. Approximately 1800 evaluable subjects will be entered into the study within 12 to 18 months at 10 participating clinical centers located around the country. At each center, subjects will be randomly allocated to intervention (10 mg/day) or control (placebo) groups.

Vitamin A and its analogs, collectively known as retinoids, have been actively studied for several years in relation to their requirements in normal physiology and health, as well as for their potential in prevention of human disease. This vitamin is necessary for the differentiation of epithelial cells and is essential for the development and function of growth, reproduction, and vision. Deprivation or deficiency of vitamin A promotes tissue metaplasia and neoplasia in various animal and organ culture models. Supplementation with retinoids can reverse these changes and restore functions of cell growth and differentiation in various cell lines.

Laboratory experiments have shown that retinoids administered to animals can prevent chemical carcinogenesis. Since in most of the experiments animals were administered retinoids after their exposure to the carcinogen, the prophylactic effect of the retinoids is believed to be in the post-initiation phase, i.e., during promotion of carcinogenesis. In addition, several epidemiological studies have shown an association of low dietary intake or serum levels of vitamin A with increased risk of cancer, notably lung cancer and other tumors of epithelial origin. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinomas for four years in patients at high risk of developing new tumors.

NHANES I Epidemiologic Follow-up Survey: Chemoprevention/Nutrition Aspects

(Z01 CN 00104 CPSB)

The purpose of the NHANES (National Health and Nutrition Examination Survey) Initial Epidemiologic Follow-up Survey was to conduct a longitudinal study of 14,407 adults originally surveyed in 1971-1975, to investigate subsequent health and mortality outcome. Respondents were traced and re-examined. Information was obtained from hospital records, the National Death Index and death certificates. The NHANES Initial Follow-up Survey is essentially complete. The purpose of this intramural project is to examine the relationship of chemopreventive and nutritional factors and cancer in the very large representative population which NHANES offers. It provides an opportunity to examine these factors and potentially confounding or modifying factors in a prospective fashion, and to examine the effectiveness or toxicity of some dietary agents which are currently of great interest for cancer prevention. The relationship of baseline vitamin use, biochemical or nutritional measures, and subsequent health status will be examined. In addition, descriptive data and trends in potential risk factors or protective factors over time will be examined. A continued follow-up for this cohort is expected to begin in 1985.

PLANS

Hypothesis-generating studies will be expanded to include: support for the continued follow-up of NHANES I; studies of the natural history of benign breast disease and breast cancer and their interrelation, the genetics of breast cancer, and dietary factors and breast cancer; linkage of Surveillance Epidemiology and End Results program data to national survey data (such as the Health Interview Survey) to study the influence of health-related habits on cancer.

Evaluations conducted to support intervention studies will be continued and expanded. These include: pharmacokinetic studies of beta-carotene, studies of the effect of dietary fat on hormonal variation and fecal mutagens, additional studies of the toxicity of new chemopreventive agents in humans, and an analysis of biologic specimens in trial participants for selected micronutrients.

New controlled intervention studies will be initiated including the use of micronutrients to prevent development of primary hepatocellular carcinoma in persons who are hepatitis B carriers, and the further study of micronutrients to prevent lung cancer in populations at high risk. As the results of controlled intervention studies become available, CPSB anticipates that more effort will be devoted to the application of these results to defined populations and the development of demonstration projects to affect reduction in cancer incidence and mortality.

STAFF

Acting Branch Chief: William D. DeWys, M.D.

Acting Deputy Branch Chief: Philip R. Taylor, M.D., S.M.

Senior Staff Fellow:	Demetrius Albanes, M.D.
	Christine Carter, Ph.D., M.P.H. Kathy J. Helzlsouer, M.D. Marc S. Micozzi, M.D., M.Sc. Arthur Schatzkin, M.D., Dr.P.H.
Senior Investigator:	Earl Gross, M.D.
Staff Fellow:	Yvonne Jones, Ph.D.
Pharmaceutical Research Coordinator:	Joseph A. Tangrea, M.P.H.
Research Study Coordinator:	William Campbell, R.N.
Research Associate:	Jan Morgan, R.Ph.
Secretarial Support:	Laura Garrison Kevin Stephenson

Cancer Detection Branch

OBJECTIVES

The objectives of the Cancer Detection Branch (CDB) are to:

- Identify new research findings that are of importance for early detection of cancer;
- Plan and conduct applied research necessary to further develop and ensure sensitivity, specificity, validity, and safety of measures for the early detection or diagnosis of cancer and to evaluate such programs when applied to defined populations;
- Plan and conduct research to analyze, evaluate, and refine cancer detection and diagnosis strategies to assure maximum benefits to the largest possible population with the least risk and cost;
- Conduct research on evaluation of cost/benefit or risk/benefit of early detection interventions and the means for quality control and monitoring of screening activities;
- Conduct studies that permit application of early detection interventions to the general population.

OVERVIEW

Formal planning for the NCI screening/detection program is in progress. The Cancer Detection Branch will respond to the thrust and guidance from those plans. As the formal plan is developed, the interactions among the three divisional program areas will expand. Within the Prevention Program there will be substantial interaction with the Occupational Cancer Branch. There is already a program interchange between the Centers and Community Oncology Program and the Cancer Detection Branch in the radiation physics area. As screening programs are developed, there will be cooperative and collaborative efforts with the Cancer Control Science Program, particularly the Health Promotion Sciences and Cancer Control Applications Branches. Interactions with the Screening Section of the Operations Research Branch will also increase. The accomplishments and highlights of the current efforts are described below.

ACCOMPLISHMENTS

Breast Cancer

The Cancer Detection Branch has continued its support of studies and analyses in breast cancer screening.

Descriptive analyses of the data collected during the Breast Cancer Detection Demonstration Project (BCDDP), which ended March 1981, have continued.

An update to the summary report published in the July/August 1982 "Ca-A Cancer Journal for Clinicians" will be published in Cancer after review by the NCI. Three additional manuscripts are currently being prepared for publication on specific portions of the BCDDP database. The data collection and validation are complete and data tapes are being prepared.

The Breast Screening Long-Term Follow-Up Study involves 64,185 women of the more than 280,000 women who are enrolled in the BCDDP. The follow-up population includes women with breast cancer; women with benign breast disease; normals matched to the benign cases by age, date of entry, geographic location of the project, and race; and women for whom a recommendation was made for surgical consultation, but aspiration or biopsy was not done.

The 28 interview center contractors are in either their fourth or fifth year of the five-year follow-up. Overall, the follow-up has been very successful, with a 97.5 percent success rate. Baseline (initial) interviews have been completed with 61,146 of the participants; 2,067 are deceased, and 1,533 have not been interviewed (interview was delayed, participants refused, or could not be located).

The plan for an extensive evaluation during the fourth year has been initiated with the establishment of an analysis and publication committee to determine if the five-year period will be sufficient to obtain optimal information from participants, and to provide direction for future analyses.

The Breast Screening Long-Term Follow-Up provides an excellent opportunity to determine estimates of risk and provides detailed information on the biology and natural history of breast disease for specific defined groups within a screened population.

A study to determine the predictive value of the Wolfe classification of parenchymal patterns on mammography will be completed in 1984. The initial phase of the study, to determine the ability of radiologists to reproducibly and consistently classify mammograms into the Wolfe categories, has been completed and found to be satisfactory. The reproducibility and consistency study has been published in The Journal of Roentgenology (Vol. 140, 1983). Other analyses proposed for the data accumulated will include interactions of the Wolfe classification with other breast cancer risk factors such as parity, age at first live birth, and family history.

A workshop is being planned that will address several issues relevant to the breast cancer screening and follow-up data. Consideration will be given to deriving high-priority analyses of the data as they exist, and determining what analyses can be addressed, if there is further long-term follow-up beyond 1986. Hypotheses will also be developed with respect to prevention intervention studies that could be done in the follow-up cohort.

Colorectal Cancer

The Cancer Detection Branch has several studies in the early detection of colon cancer.

A large cancer control program, titled "Detection of Early Colon Cancer," is in its final year. This clinical trial on the efficacy of screening for colorectal cancer evaluated the value of fecal occult blood testing in screening.

This study began in March 1975 at the Strang Clinic and involved 22,500 persons. The final grant period was devoted to follow-up efforts and analysis of accumulated data. The analysis was concerned with the following: the correlation between the stage at detection of colon cancer and survival and mortality, the outcome in the hemoccult positive population, and the morbidity and mortality of patients after the removal of adenomatous polyps. It is expected that this study will contribute new knowledge about the benefit of occult blood testing in early cancer detection.

The National Polyp Study, also titled "Control of Large Bowel Cancer Following Polypectomy," examines the type and frequency of medical examination of persons who are considered to be at increased risk of colon cancer because they have had an adenomatous polyp removed. In the present practice of medicine, there is considerable variation in the frequency and method of follow-up examinations. Utilizing a randomized design, this multi-center project will provide firm data to show whether repeat examinations should be performed at one or three year intervals following polypectomy, and whether pneumocolon x-ray and/or colonoscopy should be the method of choice. The role of the fecal occult blood test is also under evaluation. Detailed pathology and other data which may produce new knowledge about the natural history of adenomatous polyps will be obtained. As of May 1, 1984, over 1,000 patients have been examined and entered into the data base. Of these, 620 have been added within the existing study groups and it is anticipated that enrollment goals will be obtained in one to two more years.

A new grant has been awarded to the Kaiser Foundation Research Institute to evaluate colonoscopy as a screening tool in asymptomatic individuals who are considered to be of high risk because they have a past history of colorectal adenomas or cancer and/or a strong family history of colorectal cancer. The relationship between the documented risk factors and specific findings on colonoscopy will be analyzed. The principal objective is to develop guidelines for the screening of high-risk subgroups. A secondary objective is to establish a control group receiving sigmoidoscopy, Hemoccult R testing and/or barium enema, but not colonoscopy. It is anticipated that a long-term follow-up study will be implemented to compare the morbidity and mortality rates in these two groups to show the long-term benefit of removal of all adenomas from the colon via colonoscopy.

Gynecologic and Genitourinary Cancer

The program for gynecologic cancer has supported projects for the study of cervical and endometrial cancers, cancers related to trophoblastic disease, and anomalies associated with in utero diethylstilbestrol (DES) exposure. All of these studies have provided insights about the nature of these cancers. Examination of the State/Territorial Health Department Cervical Cancer Screening Program (CCSP), augmented with an analysis of similar studies (the Walton Report from Canada), reveals some of the limitations of mass screening in the elimination of cervical cancer mortality. The studies on in utero DES exposure indicates that cancers occur very rarely, at least over the near term. A follow-up program is currently in place to monitor the health status of exposed and unexposed persons.

The analysis of data from the diethylstilbesterol adenosis (DESAD) study has shown that in utero DES exposure is associated with vaginal adenosis and other anatomic and histologic changes. While most cases of clear-cell cancer of the vagina have been preceded by adenosis, cases of adenosis rarely progress to cancer. Because of concern about future adverse effects, a mail follow-up of the cohort assembled by Baylor University, Massachusetts General Hospital, the Mayo Foundation, and the University of Southern California is being supported.

Program staff have examined the feasibility of a study of testicular cancer screening. Based on low incidence and decreasing mortality, a study is not likely to reach statistically significant conclusions.

Cooperative Early Lung Cancer Program

The NCI Cooperative Early Lung Cancer Detection Program was initiated in 1973 and 1974 involving four contractors (three clinical centers and one statistical center). The purpose of the program was: (1) to evaluate sputum cytology as a supplement to annual chest x-rays (2 centers) in detecting pulmonary neoplasms; or (2) to evaluate chest x-rays plus sputum cytology compared to usual medical care (1 center). The studies also assessed the efficacy of techniques for prompt localization of occult lung cancer.

Specifically, the screening program was to answer the following:

- Can the detection of lung cancer be improved by adding sputum cytologic screening to examination at regular intervals with chest x-rays?

- Can the mortality of lung cancer be reduced substantially by this type of screening program followed by localizing methods and treatment?

It was determined that, to be statistically meaningful, at least 30,000 participants at high risk of developing lung cancer should undergo regular screening for five years and be followed for at least five years thereafter. (High-risk population was defined as asymtomatic males over 45 years old who smoked at least one pack of cigarettes per day.) Thus, approximately 10,000 men were enrolled into each of the studies at the three clinical centers. The statistical center has been involved in this large screening program to collect and analyze information from the clinical centers. Regular Mortality Review Committee meetings are held to verify the cause of death. The program will terminate by the end of this year.

At one of the clinical centers, the total number of lung cancer deaths is lower in the sputa cytology group. Cytologic screening seems to impact only on squamous cell cancer. Overall, these studies support the conclusion that screening by sputum cytology examinations and chest x-rays followed by prompt and appropriate therapy does not reduce mortality due to lung cancer.

Atlas of Early Lung Cancer was published early this year, a result of the combined efforts of the contractors and the NCI. It is expected that prevalence articles will be published soon and incidence papers will be forthcoming. There have been numerous publications from this program.

Radiation Quality Assurance and Risk Reduction

The use of radiation in medical care is recognized as the largest man-made radiation exposure to the United States population. Diagnostic radiologic procedures have become more varied and useful in medical practice and radiation therapy is used frequently for the treatment of cancer. More than 50 percent of all cancer patients will receive radiotherapy at some time in the course of treatment. The emphasis of the Cancer Detection Branch has been not only on improvements in these diagnostic and therapeutic technologies, but also on patient protection and an avoidance of unnecessary radiation.

Significant improvements in the treatment of cancer with radiotherapy were achieved in the 1950s with the introduction of Cobalt machines and linear accelerators. Over the past decade, increasing emphasis has been given to combining radiotherapy with surgery and/or chemotherapy in order to take advantage of the benefits of each modality. There is a need for improved radiation dosimetry and treatment planning because tumors recur locally or regionally in approximately 100,000 patients each year.

The success or failure of radiation therapy can depend upon the accuracy with which the dose prescription is given. For many cancer sites the successful outcome of treatment depends upon tumor doses that do not vary by more than ±5 percent about the optimum. As the concepts of radiation dosimetry advance, and physical data and measuring instruments improve, it has become increasingly important to reduce the uncertainty in the dose for radiation therapy.

Six regional Centers for Radiological Physics (CRP) provide quality assurance activities in therapy and risk reduction in diagnostic radiology. The CRPs review physics support at all facilities in the DCPC affiliated clinical programs and serve as a resource for quality assurance, technology tranfer, and education of the radiological community. The CRP coordination program, conducted by the American Association of Physicists in Medicine, ensures national uniformity in the nature and quality of activities performed and evaluates the impact of the Centers for Radiological Physics on the cancer control effort. The purpose of these projects is to develop methods and review procedures that permit the radiological community to deliver absorbed doses more accurately than previously possible. Over 260 community facilities are reviewed and monitored on a routine basis by the CRPs. This number has increased to over 300 facilities with the addition of the Community Clinical Oncology Program (CCOP).

The CRPs have carried out 1,200 reviews of 600 different radiation generators at some 500 different facilities. These include reviews of cobalt machines, accelerators, and betatrons. The percent of facilities meeting the 5 percent tumor dose delivery criteria on the first review was 78 percent; at the time of the second review, 89 percent met the criteria. Physics reviews are conducted every two years. Evaluation of data from a third review will be completed during the coming two year period. A new protocol for calibration of electron beam energies has been developed and is presently being evaluated by the CRP program. It is expected that this new protocol will be fully implemented during the coming year.

An interagency agreement with the Food and Drug Administration (National Center for Devices and Radiological Health) was implemented during this fiscal year. The agreement provides for the conduct and support of activities for reducing unnecessary radiation to patients and improving image quality in mammography and computer tomography.

Nationwide estimates of mammography and CT equipment utilization and performance will be undertaken by the Food and Drug Administration in cooperation with State Health Departments (SHD) and appropriate professional organizations. Measurements will be made to determine exposure levels and several other parameters related to technique. The data will be analyzed for exposure and/or image quality problems. Follow-up contacts will be conducted by SHDs in order to recommend improvements. Information from these surveys will provide exposure and dose information on a voluntary basis for each participating facility and this information will be available to the public, if requested from the clinicians. Publications resulting from this study will describe the evaluation of the extent of radiation exposure to the population from mammography and computerized tomography, the overall status of equipment utilized in the country at this time, and the estimate of the number of women receiving mammography each year.

PLANS

Emphasis will be placed on the development of long range plans in detection. These plans will be presented in 1984 for implementation in 1985 and beyond. The Branch interests for FY 84 include:

- Evaluation of new screening interventions, including their net benefit to health and reduction of mortality;
- Initiation of proven screening and detection interventions in high risk groups;
- Initiation of studies oriented toward obtaining new knowledge of the natural history of disease necessary for the evaluation of screening efforts;
- Evaluation and applied research on new technology and its application to the screening of high-risk groups;
- Early detection efforts targeted toward the detection of cancers for which new therapies are proving effective;
- Continued efforts to reduce unnecessary levels of diagnostic radiation;
- Development of quality control for therapeutic radiation;
- Implementation and continuing evaluation of screening programs designed to facilitate the early detection of cancer (possibly including programs involving mammography and occult blood testing);
- Continuation of the search for new knowledge about detectable early lesions and precursors of cancer (e.g., the investigation of the poten-

tial for the reduction in mortality from melanoma through the identification of dysplastic nevi);

- Development of new modalities and refined methods to be applied to the detection of early disease in asymptomatic persons (e.g., studies to evaluate NMR as an alternative or adjunct to the early diagnosis of breast cancer);
- Exploration of the feasibility of screening with NMR for early lesions in other organs, if suitable high-risk individuals can be identified;
- Initiation of efforts to establish criteria for quality control in oncological pathology, including standardization of procedures, diagnostic criteria, and nomenclature;
- Initiation of studies to compare the performance of automated instruments and conventional manual examination procedure in the screening of cells from the female genital tract for early detection of cervical cancer.

STAFF

Chief: Richard D. Costlow, Ph.D.

Program Director: Robert T. Bowser, Ph.D.
Bill Bunnag, Ph.D.
Dorothy R. Brodie, M.D.

Secretarial Support: Mickey Hanna
Lennita R. Loftin

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Centers and Community Oncology Program

Associate Director's Report

The Centers and Community Oncology (CCO) Program supports shared research resources in cancer centers and applied research resources in the delivery of treatment, continuing care, and rehabilitation of patients with cancer. Within the Division of Cancer Prevention and Control (DCPC), the CCO Program provides the framework for the integration of cancer centers and community activities. The CCO Program also has the responsibility of stimulating, developing, applying, and disseminating knowledge and technology related to cancer patient management.

Specifically, the CCO Program is responsible for:

- Promoting activities to integrate and consolidate resources in cancer centers;
- Constructing and renovating cancer research facilities through grant supported programs;
- Linking cancer centers and community hospital resources;
- Increasing the involvement, education, training, and interactions of community physicians and other professionals interested in improved cancer care;
- Extending the knowledge and understanding of the causes, mechanisms, diagnosis, and treatment of the multiple forms of cancer through the application of proven technology and successful methods of cancer patient management in various community settings;
- Planning, directing, coordinating, and evaluating the application of research advances and practical cancer control interventions in the community;
- Supporting and stimulating multidisciplinary research in the areas of rehabilitation and continuing care;

- Stimulating integrated research, both basic and clinical, on specific cancers (e.g., breast, large bowel, pancreas, prostate, and urinary bladder);

- Defining applied research opportunities derived from integrated organ site research and accelerating the progression from research to application.

The extramural research efforts of CCO are conducted through three separate, but interdependent, units: the Cancers Centers Branch, the Research Facilities Branch, and the Community Oncology and Rehabilitation Branch. By implementing proven technology and successful methods of cancer patient management in various settings, increasing the involvement of health care professionals in the community, and transferring the therapeutic experience gained from the NCI's past and present research efforts, programs of the CCO attempt to reduce the impact of cancer on our nation's population.

OVERVIEW

Cancer Centers in the CCO Program serve as lead organizatons in performing research in basic and clinical areas; provide specialized research and clinical capability in selected areas of interest and competence; serve as focal points for testing and evaluating management methods, especially new treatment approaches; and transfer effective research efforts into medical practice.

CCO-supported research focuses on:

- The participation of physician oncologists in clinical research in the community, while applying current cancer management knowledge;

- The creation of solutions to common continuing care problems associated with cancer, including pain control, rehabilitation, caring for patients with advanced cancer and their families, and preserving quality of life to the extent possible;

- The relationship of patient and professional knowledge and attitudes to the behavior of physicians, nurses, and other health professionals in caring for cancer patients;

- The identification of social, economic, emotional, and physical burdens which cancer creates for patients and their families.

In addition, specific organ systems (e.g., cancers of the large bowel, pancreas, prostate, urinary bladder, and breast) have been designated for targeted research because of their prevalence and the need for more research activity. Other organ systems may be considered for future efforts (e.g., brain). The strategy is to promote basic and applied research on the full spectrum of prevention, diagnosis, treatment, rehabilitation, and continuing care for these selected cancers.

HIGHLIGHTS

In the past year, a review of the Cancer Centers Program was initiated for the purpose of characterizing centers according to research activities and resources. Also, a series of cancer center planning meetings were held to discuss and develop ways in which centers can collaborate or interact with one another for their mutual benefit and the benefit of their regional constituents. The President's Cancer Panel has also been addressing cancer centers' issues and will continue to do so over the next two years. The potential for expanding the role of cancer centers in the area of cancer control was addressed, as was the feasibility of sharing resources among centers as a means of making the best use of new technologies available to some centers. The specific role of centers in regional cancer prevention and management efforts is yet to be defined.

In FY 84, the CCO Program held several workshops which focused on selected areas of cancer treatment, rehabilitation, and continuing care. Workshop topics included Head and Neck Cancer: Integration of Treatment and Rehabilitation, Focus on Cancer Survivors, and Research Priorities for Cancer Nursing.

Studies have begun under the "Patterns of Care for Elderly Cancer Patients: Implications for Cancer Control" research initiative. Eleven projects are being supported to study various interrelationships between cancer and aging, including how physiological, epidemiological, psychological, and economic factors influence the treatment and care of elderly persons diagnosed with cancer. This research effort represents mutual concerns of both the National Cancer Institute and the National Institute on Aging (NIA). Two grants are NIA awards.

A descriptive follow-up study of the NCI's Training Program for Maxillofacial Prosthodontists and Maxillofacial Dental Technicians was completed. The training program, which was active from 1973 to 1982, provided resources to seven training institutions to help dentists and dental technicians to become more involved in the treatment and rehabilitation of patients with head and neck cancer. The follow-up investigation developed a descriptive profile of the dental practice activities of past NCI-sponsored trainees. This study served as a model for the internal review of a previously supported program.

The Community Clinical Oncology Program (CCOP), begun in 1983, is a significant part of CCO's effort to incorporate cancer research findings and clinical trials into community-level medical practice. Community physicians work with regional cancer centers or national cooperative cancer groups in placing cancer patients on protocol studies. This is an important and innovative cancer control effort consisting of 62 CCOPs which include 189 hospitals.

The Community Hospital Oncology Program (CHOP), consisting of 17 projects, completes the implementation phase at the end of this fiscal year. CHOP activities are to be carried out with local community support.

Presently, the Community Cancer Care Evaluation project is studying three programs (the Cooperative Group Outreach Program, the Community Hospital Oncology Program, and the Community Clinical Oncology Program) to determine their level of success (independently and in collaboration with one another) in effecting change in cancer care in the community setting.

PLANS

The CCO Program will continue to explore opportunities and create means to integrate community and cancer center research activities. The goal is to increase the prospects of facilitating the transfer of research findings from the cancer centers to application in the community exploiting patient resources and physician interests to establish firm links between centers and communities.

The CCO Program plans to expand its activities in the areas of continuing care and rehabilitation for persons with cancer. Its aim is to identify and/or develop effective ways to lessen or eliminate the problems or negative consequences that may arise for cancer patients and their families. Studies that identify and address the concrete needs of cancer patients will be solicited through the RFA mechanism later in this calendar year. Pain management, quality of life issues, and oncology nursing are other targets for CCO Program attention.

ORGANIZATIONAL CHANGES

This year the Organ Systems Program was designated a section within the Cancer Centers Branch. The organizational change will enhance the research effort on specific organ systems within the cancer centers. Through a competitive award and under the cooperative agreement mechanism, an Organ Systems Coordinating Center was established in late FY 84 to replace the four organ site headquarters which previously administered the large bowel, pancreas, prostate, and urinary bladder cancer programs. The Coordinating Center provides administrative support to five working committees charged with developing priorities for disease-oriented research efforts in cancers of the breast, large bowel, pancreas, prostate, and urinary bladder. NCI program staff and the Organ Systems Coordinating Center personnel will work together to ensure an effective targeted disease effort.

STAFF

Associate Director:	Jerome W. Yates, M.D., M.P.H.
Assistant Director:	Rosemary Yancik, Ph.D.
Technical Assistant:	Anne Middleswarth
Secretarial Support:	Marilyn Goldberg M. Judith Uyehara Irene Randell

Cancer Centers Branch

OBJECTIVES

The Cancer Centers Branch (CCB) is one of three branches in the Centers and Community Oncology Program. The objectives of the CCB are to:

- Develop, direct, and administer a program of core support grants for comprehensive and specialized cancer centers;
- Evaluate the effectiveness of the Cancer Centers Program;
- Identify as components of the Centers' programs the cancer-related basic and clinical projects in other NCI divisions and coordinate branch activities with related activities;
- Present grant applications and provide special reports, as required, to the National Cancer Advisory Board;
- Maintain liaison with appropriate Federal and non-Federal organizations, institutions, and scientists;
- Facilitate the integration of the cancer center network and research on specific organ systems.

OVERVIEW

A Cancer Research Centers program was initiated in 1961 to provide grants for the support and development of cancer programs which engage in clinical and basic (laboratory) research, to search for and discover ways to improve the diagnosis and treatment of cancer patients, to train an effective group of physicians and scientists for the future, and to hasten the adoption of the best cancer management in the community.

Later, a greater emphasis was placed on programs of broad scope which could provide a comprehensive multidisciplinary attack on cancer problems. The National Cancer Act of 1971 and the National Cancer Act Amendments of 1974 provided for the establishment of additional cancer centers, resulting in a significant increase in the number of cancer centers and diversification in their functions in the 1970s.

Cancer Centers have developed in a number of different organizational settings. Some are independent, freestanding institutional entities; others are under the auspices of universities; still others are consortia, or multi-institutional in nature. Although any Cancer Center needs a certain minimum number of research programs for a "critical mass," Cancer Centers vary greatly in size and breadth of programs. Depending on areas of existing strength, they encompass a variety of activities, from highly specialized and narrowly focused programs to broad, coordinated, multifaceted programs. As a national resource, Cancer Centers provide a milieu which fosters the generation and transfer of new knowledge through its support of highly trained laboratory and clinical research personnel, physical facilities and equipment, and administrative structures. New developments in cancer prevention, diagnosis, treatment, rehabilitation, and continuing care are ultimately destined for adoption by health professionals and the general public in communities around these Centers.

Cancer Centers are classified as: Laboratory Cancer Research Centers (LCRC)--centers engaged only in laboratory research, or Clinical Cancer Research Centers (CCRC)--centers engaged in both laboratory and clinical research. In addition, CCRCs with a funded Cancer Center Support (Core) Grant (CCSG) may apply to the NCI for recognition as a Comprehensive Cancer Center. Such recognition may be granted by the Director of the NCI if the Center complies with the guidelines for comprehensiveness established by the National Cancer Advisory Board and revised by the Board in 1979.

In July 1984, 54 Cancer Centers had core grants, 15 of which were Laboratory Cancer Research Centers. Of the remaining 39 Centers, all of which combine both basic and clinical research programs, 20 have been designated as Comprehensive Cancer Centers and 19 as Clinical Cancer Research Centers. Centers are listed by type on the pages which follow; their locations are shown on the accompanying map (see Figure 9).

Although Cancer Centers' activities are supported by both Federal and non-Federal funds, a major portion of their total financial support is from the NCI. An important funding mechanism is the Cancer Center Support (Core) Grant available through the Cancer Centers Branch, NCI. All Cancer Centers are eligible for a core grant. Applications undergo competitive scientific and technical review according to the prescribed peer review procedure of the NIH.

The purpose of a CCSG is to support the planning, development, evaluation, administration, and maintenance required to consolidate and focus cancer-related activities in a single administrative and programmatic structure. The CCSG may support salaries for key professional and administrative personnel, shared equipment, special facilities and services, alteration and renovation, and developmental research activities.

A unique and important feature of the CCSG is the provision of funds for major equipment and shared resources and services not available from other grant programs. Such shared resources may result in a cost saving to the Center and, therefore, to the National Cancer Program. Specific examples of shared resources include media preparation, glassware washing, animal colony central services, and clinical research bed units. Usually, for these shared resources and services, only costs for centralized services are charged to the CCSG. Costs directly related to individual research projects are charged to the applicable project.

It is important to emphasize that, except for developmental projects, research itself is not supported by the CCSG. The CCSG provides only a minor portion of total support for the Centers. The major portion of Cancer Center research is funded by combinations of individual research grants, clinical and basic program project grants, cancer control grants, clinical education and training grants, fellowships, contracts, and various funds received from other Federal, non-Federal, and local sources.

COMPREHENSIVE CANCER CENTERS

1. Comprehensive Cancer Center
   University of Alabama in Birmingham
   Birmingham, AL

2. Kenneth Norris, Jr. Cancer Research Institute
   University of Southern California
   Comprehensive Cancer Center
   Los Angeles, CA

3. Jonsson Comprehensive Cancer Center
   UCLA Medical Center
   Los Angeles, CA

4. Yale University Comprehensive Cancer Center
   Yale School of Medicine
   New Haven, CT

5. Georgetown University/Howard University Comprehensive Cancer Center

   Vincent T. Lombardi Cancer Research Center
   Georgetown University Medical Center
   Washington, DC

   Cancer Research Center
   Howard University Hospital
   Washington, DC

6. Comprehensive Cancer Center for the State of Florida
   University of Miami Hospital & Clinics
   Miami, FL

7. Illinois Cancer Council
   Chicago, IL

   Northwestern University Cancer Center
   Chicago, IL

   University of Chicago Cancer Research Center
   Chicago, IL

8. Johns Hopkins Oncology Center
   Baltimore, MD

9. Dana-Farber Cancer Institute
   Boston, MA

10. Comprehensive Cancer Center of
Metropolitan Detroit
Detroit, MI

11. Mayo Comprehensive Cancer Center
Rochester, MN

12. Memorial Sloan-Kettering Cancer
Center
New York, NY

13. Roswell Park Memorial Institute
Buffalo, NY

14. Columbia University Cancer Center
College of Physicians & Surgeons
New York, NY

15. Comprehensive Cancer Center
Duke University Medical Center
Durham, NC

16. Ohio State University Comprehensive
Cancer Center
Columbus, OH

17. Fox Chase/University of Pennsylvania
Comprehensive Cancer Center

Fox Chase Cancer Center
Philadelphia, PA

University of Pennsylvania Cancer Center
Philadelphia, PA

18. University of Texas System Cancer Center
M. D. Anderson Hospital & Tumor Institute
Houston, TX

19. Fred Hutchinson Cancer Research Center
Seattle, WA

20. University of Wisconsin Clinical Cancer
Center
Madison, WI

CLINICAL CANCER CENTERS

1. University of Arizona Cancer Center
   University of Arizona College of Medicine
   Tucson, AZ

2. Northern California Cancer Program
   Palo Alto, CA

3. UCSD Cancer Center
   University of California at San Diego
     School of Medicine
   La Jolla, CA

4. Cancer Research Center
   Beckman Research Institute of
     the City of Hope
   Duarte, CA

5. Cancer Center of Hawaii
   University of Hawaii at Manoa
   Honolulu, HI

6. University of Iowa Cancer Center
     College of Medicine
   Iowa City, IA

7. Norris Cotton Cancer Center
   Hanover, NH

8. Mt. Sinai School of Medicine
   New York, NY

9. Cancer Research Center
   Albert Einstein College of Medicine
   Bronx, NY

10. New York University Medical Center
    New York, NY

11. University of Rochester Cancer Center
    Rochester, NY

12. Lineberger Cancer Research Center
    University of North Carolina
    School of Medicine at Chapel Hill
    Chapel Hill, NC

13. Oncology Research Center
Bowman Gray School of Medicine of
Wake Forest University
Winston-Salem, NC

14. Puerto Rico Cancer Center
University of Puerto Rico
San Juan, PR

15. Brown University
Roger Williams General Hospital
Providence, RI

16. St. Jude Children's Research Hospital
Memphis, TN

17. UTMB Cancer Center
University of Texas Medical Branch
Galveston, TX

18. Vermont Regional Cancer Center
University of Vermont
Burlington, VT

19. Massey Cancer Center
Medical College of Virginia
Virginia Commonwealth University
Richmond, VA

LABORATORY CANCER CENTERS/BASIC

1. Cancer Research Center
   La Jolla Cancer Research Foundation
   La Jolla, CA

2. Armand Hammer Center for Cancer Biology
   The Salk Institute
   San Diego, CA

3. California Institute of Technology
   Biology Division
   Pasadena, CA

4. Cancer Research Center
   Purdue University
   West Lafayette, IN

5. The Jackson Laboratory
   Bar Harbor, ME

6. Worcester Foundation for Experimental Biology
   Shrewsbury, MA

7. Massachusetts Institute of Technology
   Cambridge, MA

8. Grace Cancer Drug Center
   Roswell Park Memorial Institute
   Buffalo, NY

9. Institute of Environmental Medicine
   New York University Medical Center
   New York, NY

10. American Health Foundation
    New York, NY

11. Specialized Cancer Research Center
    Case Western Reserve University
    Cleveland, OH

12. Cancer Research Center
    Pennsylvania State University College of Medicine
    Hershey, PA

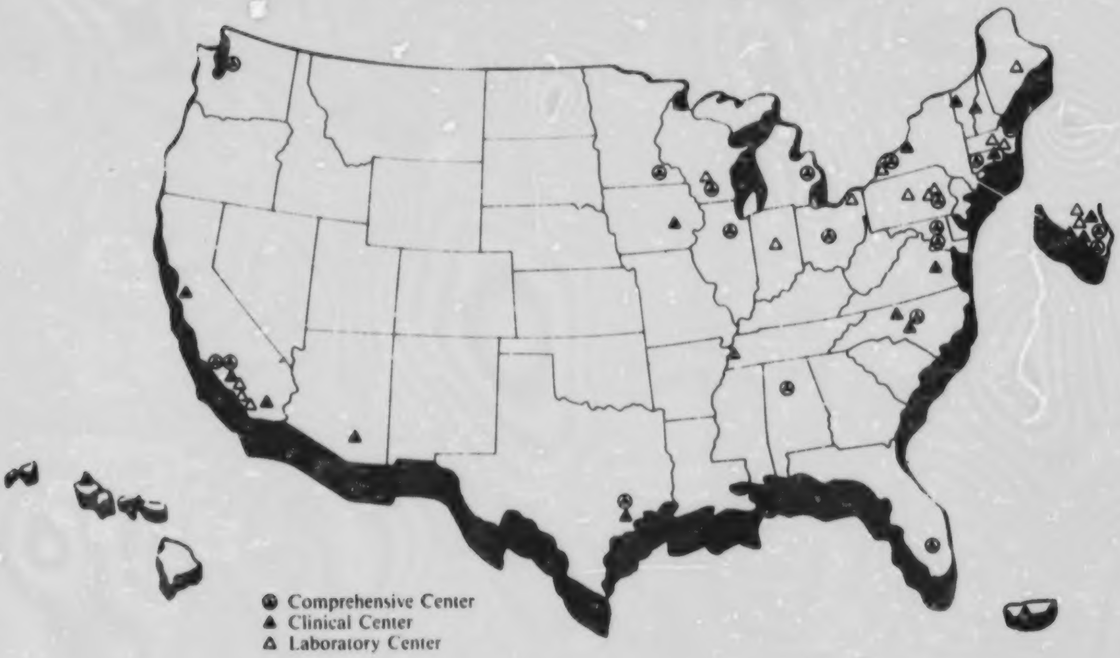
13. Wistar Institute of Anatomy and Biology
    Philadelphia, PA

14. Fels Research Institute
Temple University School of Medicine
Philadelphia, PA

15. McArdle Laboratory for Cancer Research
University of Wisconsin
Madison, WI

FIGURE 9

Location of Cancer Centers


● Comprehensive Center
▲ Clinical Center
△ Laboratory Center

ACCOMPLISHMENTS

More than one-half of the NCI funds in support of extramural research projects are awarded to institutions which also receive Cancer Center core grants. As a consequence, a multitude of research accomplishments could be cited since the core grant funds impact directly on this research through support of various shared services and facilities in the Centers and by increasing interdisciplinary activities.

Some general areas which receive particular attention at Centers include oncogene research, the use of monoclonal antibodies for aspects of diagnosis and treatment, various approaches to cancer prevention, developmental chemotherapy, chemical and environmental carcinogenesis, and new methods in cancer control research.

Centers continue to play a major role in the National Cancer Program. They are designed to promptly apply research findings to clinical and community situations and, thus, are a critical part of the network of activities which will achieve reductions in mortality from cancer. Ongoing review by the President's Cancer Panel includes questions about future directions for the Cancer Centers Program and how the research organizations can interface with their communities in helping to find solutions to cancer-related societal issues.

During the past year the Centers and Community Oncology (CCO) Program has conducted a series of meetings to formulate future plans for the Cancer Centers' activities. Topics discussed have included: (1) the growing need for upgrading and replacing research facilities and equipment; (2) how to replace key Center leaders who will retire in the next ten years; (3) the need for additional support for data management requirements of clinical research; and (4) the number and types of centers that should be supported to direct adequate attention to regional and minority needs. Particular attention is being given to defining the role of the Centers in achieving the NCI goal for the year 2000.

PLANS

The planning activities mentioned above should provide new directions for the program in the coming year. It is expected that efforts will be made to: (1) increase the number of traditional centers supported by core grants; (2) explore the possibility of Center development in institutions relating to minority populations and/or geographic regions currently without Centers; and (3) exploit the linkages of networks of Centers for targeted intercenter collaborations.

Several multicenter collaborative efforts will be underway in the next fiscal year. For example, collaborative intercenter research to coordinate protocol development for nuclear magnetic resonance (NMR) imaging will commence. This activity has the potential of improving the flow of information while limiting duplication in research efforts.

To promote and facilitate collaboration in special research studies, ways of more precisely characterizing Cancer Centers and their resources also will be studied.

ORGANIZATIONAL CHANGES

In FY 84, the Organ Systems Program was designated a section within the Cancer Centers Branch. A description of that program's activities for the year follows.

ORGAN SYSTEMS SECTION

Objectives

The Organ Systems Section implements the Organ Systems Program. In support of DCPC's overall goal to reduce cancer incidence, morbidity, and mortality, the objectives of the Organ Systems Program are designed to:

- Encourage accomplished investigators to study cancer in specific organ systems,
- Foster multidisciplinary collaboration in studying specific organ system cancers,
- Recruit scientific and administrative expertise from the biomedical community for planning and implementing targeted research.

Overview

The Organ Systems Program consists of grant-supported projects of targeted cancer research, each a planned research effort involving cancer at a specific organ site. These projects have been concerned with cancers of the breast, large bowel, pancreas, prostate, and urinary bladder. This program was implemented by the National Cancer Institute during the past decade to foster and stimulate interdisciplinary research aimed at cancers of certain organs where the level of research activity has not been commensurate with a public health problem posed by the diseases. Having attracted new investigators, the programs succeeded in stimulating new research in these areas.

The Organ Systems Program is advised by five working groups: breast, large bowel, pancreas, prostate, and urinary bladder. Each working group is responsible for planning, coordinating, monitoring, and evaluating the epidemiologic, laboratory, and clinical research components of these programs. Interaction and communication among these components is fostered through workshops, conferences, and other mechanisms, as appropriate. As areas for new research initiatives are identified, they are organized into program announcements, Request for Grant Applications (RFA), or Request for Contract Proposals (RFP), depending on the mechanism most appropriate to achieve the program goals.

Each Organ Systems project sponsors and encourages laboratory and clinical research directed toward improving the techniques available for detecting and diagnosing, treating, and ultimately preventing or controlling cancer at the particular organ sites. This charge requires the development and use of effective planning and management systems to stimulate, encourage, coordinate, and facilitate individual and collaborative investigation from all disciplines of biomedical science, while maintaining a focus on the course of disease. This is done through various forums ranging from small meetings and conferences to major workshops. Investigators are encouraged to submit grant applications to accomplish the program objectives.

Accomplishments

Representative highlights of the accomplishments of grantees supported through each program over the past year are presented below.[1] These summaries are organized by research area under each organ site project.

Bladder Cancer Project

Carcinogenesis and Tumorigenesis

Several studies are ongoing to investigate the steps involved in the initiation, promotion, and progression of bladder cancer.

Studies were performed to examine the cell kinetics of early changes in promotion by sodium saccharin. It was shown that the administration of sodium saccharin immediately after induced ulceration, or beginning two weeks later, results in a prolongation of the marked hyperplasia that would result from ulceration alone. Further, if sodium saccharin is delayed until eight weeks after ulceration, when the bladder has returned to normal by histological standards, the marked hyperplasia recurs.

A short-term study to test the induction of hyperplasia by nitrofurantoin produced results consistent with previous findings that nitrofurantoin is neither a complete carcinogen nor a promoting agent.

Other studies have demonstrated that urothelial cells from human patients and from several animal species respond similarly to urinary metabolites of arylamines. This suggests that hydroxylamines, hydroxamic acids, and the N-glucuronic acid conjugates of hydroxylamines may be the active urinary metabolites of arylamines that induce bladder cancer.

FANFT (N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide) is a wellknown carcinogen which produces a high incidence of urinary bladder tumors in several species. It is metabolized to ANFT (2-amino-4-(5-nitro2-furyl) thiazole) and is excreted as such in several species of rodents. ANFT has been tested previously for its carcinogenicity in mice, where it produced tumors in the forestomach, but not in the bladder. A recent study shows that ANFT fed to rats for 52 weeks produces a variety of tumors, including papillomas and carcinomas in the bladder. These studies point out an additional species difference in carcinogenic susceptability and affirm a probable role for ANFT in the induction of rat bladder tumors by FANFT feeding.

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[1] References are available upon request from the Organ Systems Section Office.

Primary cultures of rat urothelial cells were exposed to NQO (4nitroquinoline 1-oxide) or HAQO (N-hydroxy-4-aminoquinoline 1-oxide) in serum-free media. Both produced unscheduled DNA synthesis. Dicumarol, an inhibitor of NQO nitroreductase, inhibited the activity of NQO and, to a lesser extent, HAQO. Pyrophosphate, an inhibitor of seryl-AMP synthetase, inhibited the activity of both compounds, supporting the hypothesis that nitroreductase and seryl-AMP synthetase may be involved in the activation of NQO.

Another long-term feeding study in which aspirin was co-administered to FANFT-fed rats showed that the incidence of bladder carcinomas in the group fed 0.5 percent aspirin plus 0.2 percent FANFT (37 percent) was significantly less than in the group fed FANFT only (87 percent). Aspirin is a well-known inhibitor of PHS (prostaglandin H synthase). This result is consistent with the hypothesis that PHS is involved in the metabolic activation of certain bladder carcinogens.

Methods have been developed for the cultivation of normal human urothelium which are quantitative and reproducible. Confluent cultures of normal transitional cells can be routinely maintained on collagen substrates for several months. These cells have been characterized, and they retain ultrastructural features characteristic of normal adult human urothelium. Altered growth characteristics of papillary transitional carcinoma cells under the same culture conditions have been identified. Multicellular, multilayered structures form in vitro which resemble the in vivo formation of papillary growths in the bladder.

Two urinary components have been isolated which are capable of inducing a marked ODC (ornithine decarboxylase) activity in a bladder cancer cell line. Both components have an apparent molecular weight of over 100,000 and consist of 90 percent protein and 10 percent carbohydrate. Both active components are resistant to heat denaturation.

In an effort to understand the metastatic process in the bladder, studies are in process to determine how proteases facilitate the tumor cells to penetrate connective tissue. In malignant rat bladder carcinomas induced with the chemical carcinogen FANFT, three types of proteolytic activities have been identified: a collagenolytic activity, a catheptic activity, and a caseinolytic activity. These may act individually or in concert to reduce the physical resistance of the host tissue.

Studies are in progress placing emphasis on generating cell lines with different oncogene content by cloning the original cell lines and by applying various selective pressures on them under various in vivo and in vitro conditions.

Immunology

Studies are underway to develop monoclonal antibodies to both animal and human bladder tumors, to define the cellular immune response, to characterize cell surface antigens, and to define profiles of blood-group related cell-surface antigens for the purposes of improving approaches to diagnosis, prognosis, and treatment.

A series of monoclonal antibodies was used to characterize the surface phenotype of a naturally occurring E+ B14-specific supressor cell present in the blood of patients with recurrent superficial bladder carcinomas. This unique naturally occurring supressor T cell has a phenotype similar to that of other supressor cells in humans, adding validity to the concept of functionally distinct T cell compartments in human blood.

Four bladder carcinoma antigens have been detected which are potentially important diagnostic markers and therapeutic targets. One of the antigens, a 200,000 MW protein, is almost exclusive to bladder carcinoma.

Two monoclonal antibodies, obtained by fusing a non-secreting myeloma cell line and spleenocytes from mice immunized with a human transitional cell carcinoma cell line, have been established and characterized. They were shown to bind selectively to human transitional cell carcinoma either on established cell lines or on fresh frozen sections of tissues.

Diagnosis and Treatment

Changes in flow cytometry findings have recently been shown to parallel the clinical responses of patients treated with BCG and to be indicators of downstaging as the result of irradiation. In order to improve the sensitivity of flow cytometry when using specimens with small numbers of tumor cells, a system was developed to concentrate tumor cells two- to ten-fold by gradient sedimentation.

Therapy

Photoradiation therapy after administration of hematoporphyrin derivative is being studied in animals and in cell cultures as a promising treatment for malignant bladder tumors. Formation of giant cells occurred in a majority of tumor cell cultures after exposure to hematoporphyrin derivative with light at 630 nm. The incidence of the formation of giant cells was proportional to the dosage of photoradiation. These cells are similar to those induced by X-radiation or ultrasound treatment.

Due to the expense and length of time required in the use of transplantable and primary tumor models for screening prospective antitumor drugs, an *in vitro* culture system called the *tumor colony assay* has been evaluated as a screening method for bladder cancer. The activity of eleven anticancer drugs was tested in this assay using four transplantable transitional cell

AVAILABLE

or squamous cell lines. The tumor colony assay predicted drug response accurately using methotrexate, anguidine, maytansine, and PALA. The assay had a low level of predictability for VP-16 and DDP.

Breast Cancer Program

Oncogenic Transformation

A recent finding of major significance in breast cancer research is that oncogenic transformation of cells in culture can be produced by transfection with DNA from either mouse or human mammary tumor cells. The Program is supporting the work that resulted in the isolation of the first oncogene from human mammary cells. This transforming gene has now been isolated twice; it is about two kilobases long and is in the process of being characterized. More recently, two new oncogenes from human mammary cells have been isolated in another laboratory by means of a more sensitive assay for transforming genes, using tumor development in "nude," athymic mice rather than foci of 3T3 cells. Active research is ongoing in several laboratories aimed at achieving molecular cloning of both the mouse and human mammary tumor transforming sequences, identifying the DNA sequence in both of these highly related transforming genes, exploring the integration into the normal cellular genome and the role of growth factors in the process of malignant transformation, and identifying the possible gene products of the transforming genes. Completed experiments already have described the activation of these transforming genes and the identification of an antigen associated with their expression. Cloning of these transforming sequences and identification of their gene products will clearly have major significance for molecular biology and for human breast cancer. Monoclonal antibodies to an activated, mutant ras oncogene protein have already been prepared, and human breast tumors are being tested for positivity to this reagent.

Genetic Susceptibility to Human Breast Cancer

Considerable interest exists in whether one or more major genes for susceptibility to human breast cancer influences the distribution of the disease, in at least a proportion of the population, and whether it can be identified. In certain breast cancer prone families, the disease appears to segregate as a Mendelian trait, and in some such families, occurrence of the disease appears to be linked to a known marker on a human chromosome, namely GPT-1 (glutamine pyruvate transsaminase). This suggests that a gene for susceptibility, located at a specific locus, may be operative in certain breast cancer prone families. This is probably not the only gene affecting risk for breast cancer, and active research is being supported to search for such genes and for a linkage relationship between such genes and with any of a wide range of defined genetic markers, which could pinpoint their chromosomal locations. The Program has an existing Program Area Announcement on research in this area, and has funded several excellent applications. There is increasing interest in DNA sequences potentially related to human breast cancer or to breast cancer susceptibility, and additional responses are desired to probe the molecular biology of genetic susceptibility at the DNA level, including searching for possible detectable chromosomal abnormalities, and to explore mechanisms by which genetic susceptibility might be expressed. Possible phenotypic expressions could be subtle differences in hormonal profiles or presence of antigens related to mouse mammary tumor virus or coded for by other specific DNA sequences.

Epidemiologic Risk Factors for Breast Cancer and Potential Preventive Agents

The Program actively supports considerable research on risk factors for breast cancer and on the biological mechanisms by which these might be involved in initiation or promotion of tumorigenesis. Possible risk factors under current investigation include hormonal profiles; neuroendocrine factors; immune surveillance and response; lifestyle elements, especially diet (both macro and specific micronutrients); exposure to hair dyes; and use of specific medications. In addition, certain specific micronutrients are under active investigation as potential preventive agents, particularly retinoids, selenium and other vitamins and/or antioxidants. Other studies that are yielding promising results are prospectively investigating "benign" breast lesions and the subsequent development of breast cancer, with the aim of identifying factors that determine and/or detect premalignant potential. One such study has now found that the relative risk of invasive breast cancer is 4.5 in women with prior atypical lobular hyperplasia and 4.1 in those with prior atypical "ductal" hyperplasia; with a family history of breast cancer, these relative risks were increased to 9.4 and 7.6, respectively.

Etiologic, Diagnostic, and Prognostic Significance of Viral Antigens in Breast Cancer

The Program is supporting several investigations which have established that breast cancers contain antigens that cross-react with certain glycoproteins of mouse mammary tumor virus (MMTV), in particular, with the 52,000-dalton major glycoprotein (gp52), but also with other MMTV glycoproteins as well. The possibility of MMTV-related antigens as a phenotypic expression of genetic high risk has already been mentioned, and investigators are exploring the prevalence of such antigens in members of breast cancerprone families, as well as in breast cancer patients. Thus, its possible role in etiology continues to be under active study. The possibility that laboratory exposure to the virus might constitute a biohazard has even been suggested and is under study.

In preliminary studies, presence of the gp52 antigen has proven helpful in distinguishing between benign and malignant lesions in borderline cases and in identifying certain clinically occult breast cancers that have presented as metastatic lesions with a non-diagnostic pattern. This marker may also offer promise as a prognostic tool; the level of detectable antigen in the tumor appears to be higher in the most aggressive breast cancers and to correlate with a poor prognosis. Other studies have shown that a breast cancer cell line in culture contains this antigen encapsulated in virus-like particles.

Factors Affecting Prognosis

The Program has continued its investigations into those factors that have a role in determining prognosis of the cancer patient. The work has taken several different directions. One is the identification of variables that favor tumor spread and the establishment and growth of distant metastasis. Another direction is the correlation of certain tissue or circulating tumor markers with prognosis. Determining such a correlation requires longitudinal clinical laboratory studies, which are in progress. A third direction is our interest in the process of vascular and lymphatic invasion in breast cancer. Although previous studies have associated the extent of invasion with prognosis, the identification of vascular invasion by pathologists in tissue sections of the breast is extremely difficult. Consequently, the Program has issued an Announcement in order to develop novel methods to facilitate the recognition of invasion in histological sections. An overall objective is to identify those prognostic factors that are easy to measure in order to bring them into clinical use.

Biological Markers for Breast Cancer

The Program has had a long-standing interest in circulating tumor markers for breast cancer. These markers would assist physicians in the diagnosis of early cancer as well as the management of patients following treatment. A number of tissue and circulating tumor markers has recently been described. These circulating markers are found in high titer in breast cancer patients with metastasis, but are not found in non-cancerous control women or in women treated for breast cancer but without known metastasis.

Similarly, tissue markers identified by monoclonal antibodies are proving helpful for the histopathological diagnosis and classification of breast cancer. Efforts are also being made to correlate the presence or absence of certain markers with prognosis.

Mechanisms of Carcinogenesis and of Metastasis

The Program is supporting several promising studies that are exploring mechanisms of carcinogenesis in terms of dedifferentiation, and probable mechanisms of metastasis in terms of processes of cell-cell and cell-substratum interactions. Results suggest that monoclonal antibodies to surface antigens can distinguish and predict the mammary gland cells that become malignant in response to a carcinogen, and that it may well be possible to develop a library of antibodies that identify differentiation antigens. Likewise, studies of several investigators indicate that membrane adhesion glycoproteins mediate cell-cell and cell-substratum interactions and that certain of these glycoproteins are probably correlated with and involved in metastasis. The role of the extracellular matrix in tumor growth and metastasis is clearly an important and very promising area of current valuable research.

Experimental Therapeutics and Mechanisms of Action of Therapeutic Agents

A number of projects deal with the mechanisms by which endocrine or chemical treatments cause alterations in breast tumor growth, exploring specific tumor, host, or treatment factors such as cytokinetics, immunological parameters, endocrine profiles during therapy, and intratumor steroid metabolism. Studies also continue to explore new, potential therapeutic agents, with considerable recent interest being focused on anti-estrogens, both steroidal and nonsteroidal. Aromatase inhibitors inhibit estrogen synthesis by affecting the aromatization of ring A of the steroid molecule. These compounds, which cause marked regression of estrogen dependent mammary tumors in the rat (more effective than tamoxifen in this animal model), have recently been moved into clinical trials in England; preliminary results have been reported to be promising.

Project Coordination/Workshops

The Breast Cancer Task Force Committee held three meetings over the course of the year. The first of these, held in January 1984, included a workshop on the topic of The Role of Extracellular Matrix and Mammary Epithelium in Breast Cancer Growth, Differentiation, and Metastasis. The state of the art in this area was effectively summarized by the recent results presented by the participants. A second meeting, in April 1984, included a workshop on Oncogenes and Other Genetic Sequences Potentially Related to Breast Cancer. This was, likewise, a very valuable session in which an up-to-date picture of the field was presented, including important new and unpublished data from several laboratories. Also, the status of relevance for breast cancer was evaluated. A summary was prepared for publication. A third meeting was held in September 1984 in Quebec, Canada in conjunction with the meeting of the National Surgical Adjuvant Breast and Bowel Project to honor Dr. Elwood Jensen on the twentieth anniversary of his work on the estrogen receptor. This meeting included a Breast Cancer Task Force Committee workshop on Steroid Receptors and Breast Cancer, New Concepts and Techniques.

Large Bowel Cancer Project

Role of Dietary Constituents in Colon Cancer

Continued progress has been made with the identification and structural confirmation of the potent mutagen identified in human feces using a combination of chemical and spectroscopic techniques. Chemical synthesis of this mutagen found in 15-20 percent of individuals and populations at high risk for colon cancer should permit carcinogenicity testing.

Cell-free extracts of the strains of bacteria capable of producing the mutagen resulted in faster mutagen production than did whole cells. This observation indicates that the excretion of this compound by certain people is dependent upon the presence of some unknown precursor. Synthesis of various biosynthetic precursors of the mutagen is in progress. The mutagen-producing species of Bacteroides are among the most common of the intestinal anaerobes, and are present in individuals who excrete the mutagen as well as in non-excretors. The characterization of this mutagen and other fecal mutagens and testing them for carcinogenic activity is important to both the etiology and prevention of colon cancer.

In parallel studies, investigation has focused on the isolation and identification of mutagenic compounds formed during the cooking of meat and assaying these compounds for carcinogenicity. A quantitative high-pressure liquid chromatographic method for determining the content of the mutagenic compound 2-amino-3-methylimidazo (4, 5-f) quinoline (IQ) has been completed. It has been demonstrated that the fat content of meat influences IQ formation during cooking, and that certain substances, such as BHA and casein, inhibit its formation. Investigation is focused on the involvement of lipid peroxidation, which appears to be important in the eventual formation of this mutagen. Major emphasis is being focused on determining the carcinogenicity of IQ and its primary target organs as well as its metabolic pathway. The effects of dietary components previously found to have inhibitory effects on food mutagens, including indole derivatives, are also under investigation. All of these studies are potentially important in achieving the National Cancer Institute's goals for cancer reduction by the year 2000.

Mechanisms of Colon Carcinogenesis

Using molecular probes for specific genes, substantial methylation in two specific genomic regions has been observed in patients with colon adenocarcinoma and other tumor types when compared to adjacent normal tissue from the same patients. The results of studies on the methylation status of two cellular oncogenes of the ras family in colon and lung carcinomas compared with normal surrounding tissue indicate that the cHa^{ras} gene was hypomethylated. These observations are being extended to a larger number of patients and genes to determine if there is a correlation between genomic changes in methylation and tumor heterogeneity, tumor progression, and abnormal gene expression. In another study, the patterns of methylation and expression of their gene panel in different metastatic lesions and within the primary tumor itself will be compared. Studies have also been initiated using cloned nucleic acid sequences (cDNAs) as probes to analyze gene expression in colon carcinogenesis. Continued efforts should provide specific probes with which to study the role and mechanisms of changes in gene expression during transformation and carcinogenesis.

Complementary efforts are aimed at identifying and analyzing the molecular mechanisms involved in the malignant transformation of colon cells exposed to chemical carcinogens. Specific changes in nuclear protein composition and phosphorylation in the colonic epithelium of DMH-sensitive animal strains are detectable very early after carcinogen treatment. Phosphorylation of specific nuclear proteins may serve as a marker for premalignant change in colonic epithelium. An analysis of factors involved in the migration of proteins between the cytoplasm and cell nucleus studied by monitoring the redistribution of microinjected proteins in cultured cancer cells has been conducted. Evidence was obtained for the homing of high mobility group proteins to the cell nucleus. Studies of the intranuclear distribution of the histone H1^0 in HT-29 and LoVo cells showed that it was excluded from nuclei and from heterochromatic regions of the chromatin. Its appearance in the nucleus coincides with the arrest of the growth cycle of the cancer cells exposed to sodium butyrate.

Studies are also in progress to investigate the effects of diets high and low in polyunsaturated versus saturated fat on prostaglandin synthesis and fatty acid dependent procarcinogen metabolism. Fatty acid-initiated co-oxidation has been demonstrated and reported as a pathway for metabolism of some xenobiotics and carcinogens in the colon. Colonic explants from rats are being used to measure the conversion of ^{3}H-benz(a)pyrene (BP) to protein-bound metabolites. ^{3}H-BP binding to protein was stimulated by arachidonic acid and suppressed by indomethacin. These effects were positively correlated with the effects of these agents on prostaglandin E (PG) accumulation in the media. Additionally, dietary studies involving examination of different dietary fibers and other dietary components are currently under investigation.

Development of a Normal Colon-Epithelial Cell Line

An important contribution has been the development, establishment, and characterization of a primary epithelial culture from normal human adult colonic mucosal biopsies. Established lines have been developed from these primary cultures. During 27 continuous culture months, the cells remained diploid and showed no evidence of senescence. The line is currently available through the American Type Culture Collection (ATCC). Concurrently, long-term epithelial cell cultures from human fetal colon have also been established.

In addition to the 2 presumptive, normal epithelial lines derived from human colonic mucosa available through the ATCC, 35 cell lines from human colorectal tumors, 8 skin fibroblast lines from a benign desmoid tumor of an individual with Gardner's syndrome, 2 cell lines from chemically-induced colonic tumors of the mouse and guinea pig, and 3 normal rat intestinal epithelial lines are also available for distribution. Complete characterization of these lines, including isoenzymology, has been carried out. In 1983, a total of 491 cultures were distributed. Premalignant colon polyps have also been successfully cultured. These accomplishments represent an important resource for studies in many disciplines and are valuable control tissues for studies in carcinogenesis, immunology, biochemistry, and pharmacology. Thus, a spectrum of normal, precancerous, and frank carcinoma cell lines for comparative studies is now available.

Hereditary Colorectal Cancer

Investigations continue on the hereditary forms of colorectal cancer in an effort to better understand the basic mechanisms associated with these diseases and their specific relationship to colorectal cancer and associated fibroblast abnormalities. Efforts are focused on improving diagnostic criteria and identifying affected individuals in an asymptomatic stage. The effects of the tumor promoter 12-0-tetradeconyl phorbol-13-acetate (TPA) on cultured skin fibroblasts was studied on 21 members of kindred 109. Good agreement was obtained between the positive TPA tests and those kindred members of different ages carrying the gene for Gardner's syndrome. New molecular biological approaches are also being applied to the study of colonic cells derived from patients with hereditary forms of the disease. There is potential for understanding more about the initiating events, thus providing an opportunity for cancer control in this high-risk population. In related studies, increased hyperdiploidy has been considered to be an in vitro expression of some cancer prone genes in human dermal monolayer cultures. Automated assays for cellular DNA content, namely incorporation of ^{3}H-thymidine during logarithmic growth and the percent occurrence of cells with double (4N) or greater than double DNA content by flow cytometry were undertaken. Concurrence between these assays with the metaphase assay should make feasible the use of this in vitro abnormality in the identification of individuals at increased cancer risk. The identification of such individuals would make possible improved medical surveillance and better management programs.

Biochemical and Immunological Markers of Colon Cancer

The structure and immunological reactivity of colonic mucins are under investigation to determine the potential of these glycoproteins as markers of colonic tissue and colonic carcinoma in particular. Research continues on an in vitro assay using tube leukocyte adherence inhibition (LAI) and organ-specific cancer neoantigen (OSN) of colon tumors. The isolation and characterization of soluble OSN from tissue-cultured colon cancer cells and the production of monoclonal antibodies to soluble colon OSN have been achieved. The complete identification of the molecules should be useful in diagnosis and immunological treatment of colorectal cancer, and have applicability toward the goal of reducing cancer incidence.

Continuing studies have reinforced the hypothesis that at least some glycoproteins on the surfaces of colonic epithelial cells--for example, CEA and secretory component--are topologically restricted to either the microvillus surface or the basal lateral surface but are aberrantly expressed randomly on colonic cancer cells. The inability of neoplastic cells to maintain a specific polarity might be exploited for diagnostic or therapeutic purposes. Other studies have found two specific differences between normal and malignant tissues; namely, a cancer associated-mucin and the expression of an antigen which crossreacts with antibody against mouse embryo differentiation stage-specific antigen (SSEA-1). Studies on the effect of putative differentiating agents on growth properties as well as on phenotypic expression of oncodevelopmental antigens will elucidate the molecular mechanisms controlling their expression and contribute toward improved diagnosis and survival of patients with colon carcinoma.

Early during colon tumorigenesis, specific nuclear nonhistone proteins, not present in normal colon tissue, appear. Studies are in progress to determine whether nuclei and chromatin of human colon adenocarcinoma cells contain specific nonhistone proteins detectable immunologically. Antibodies to tumor-specific chromosal proteins and their complexes with DNA are being utilized as markers and to study phenotypic changes associated with chemical carcinogenesis in the large bowel. These techniques will be developed further and applied to the immunological identification of the malignant and premalignant cells in sectioned tissues of biopsies.

Prognostic Markers

Studies were carried out to define the optimum technique for preparing single cell suspensions of intact colonic epithelial cells from normal mucosa and colonic carcinoma to be studied by flow cytometry. Analysis of DNA ploidy by flow cytometry in tumors from patients stratified by Dukes' stage in two independent laboratories has shown encouraging results in terms of diagnostic and prognostic potential. A series of 33 patients has been studied for DNA content per cell measured by flow cytometric techniques from nuclei isolated from adenocarcinoma of the colon obtained at surgery. Among the 20 patients with colon carcinoma cells having diploid DNA content, 5 died with recurrent disease while 14 have remained free of the disease for at least a five year period. Of the 13 patients with nondiploid or aneuploid tumors, all developed recurrent disease within two years and only one survived beyond three years. These studies are suggestive of the prognostic value of DNA content in human colon carcinoma. In studying the pathology of colon carcinoma, it has been observed that infiltration of human colon carcinomas by eosinophils (more than 30 eosinophils/mm$_2$) is associated with a low incidence of metastasis at the time of colonic resection. Continued follow-up of the initial population of patients and the addition of more patients have confirmed this observation. The survival among these patients is improved. Studies of macrophages in colonic carcinomas are currently underway.

New Approaches to Therapy for Large Bowel Cancer

An urgent need is the development of predictable and valid *in vitro* short-term assays to evaluate therapeutic agents. The clonogenicity of human colorectal tumor stem cells is currently under investigation. It has been found that the use of August rat red blood cells in the feeder layer dramatically increases the clonal growth of the tumor cells tested. Apparently these cells possess a clonal growth-promoting factor that is still unidentified.

Using a series of six human adenocarcinomas of the colon and rectum maintained subcutaneously in immuno-deprived mice, studies are in progress to elucidate the biochemical determinants of tumor responsiveness to 5-fluorouracil (FUra) *in vivo* and to identify factors that may influence the selectivity of treatment. The insensitivity to FUra is correlated with the inability of these tumors either to form or to maintain a stable ternary complex due to low intracellular concentrations of 5,10-methylenetetrahydrofolate (CH_2FH_4).

These studies have shown that thymidylate synthase derived from FUra-sensitive tumors may possess different properties than the enzyme derived from insensitive colon xenografts. Screening of newly synthesized quinazoline congeners continues with interest focused on the 2-amino-4-hydroxy-quinazolines which are inhibitors of thymidylate synthase rather than dihydrofolate reductase. Studies have been initiated to investigate the toxicology and pharmacokinetics of a candidate compound (H-338) in the dog. Selective metabolic activation together with selective retention in tumor cells may provide certain inhibitors of thymidylate synthase with a distinct therapeutic advantage in treating tumors which are unresponsive to MTX or are 5-FU resistant. From the data to be collected in the upcoming year, it will be determined whether this drug should advance to clinical trial and what the most effective scheduling would be.

Another encouraging approach to improved treatment is the use of differentiation-inducing chemicals on human colon carcinoma cells which has utilized primarily the polar solvent, N,N-dimethylformamide (DMF) and its metabolite N-methylformamide (NMF). The latter compound has recently completed Phase I trial. Relevant observations have been made regarding the additive antitumor effect of these agents with ionizing radiation without concomitant additive toxicity.. The effect is enhanced still further when the radiation is administered on a fractionation protocol. The results strongly support the suggestion that polar solvents should be considered for use as radiosensitizing agents in combination with radiation therapy for rectal cancer. Future studies will focus on the mechanism of action of these polar solvents in the development of other classes of differentiation-inducing agents for human colon carcinoma.

Although indomethacin administered in the drinking water significantly reduced the incidence of colon tumors induced by methylazoxymethanol acetate, it has now been observed that a new class of nonsteroidal anti--inflammatory agents, piroxicam, administered in the feed has similar inhibitory effects, but is less toxic. It has also been observed that restricting the standard diet (L-485) of rats to 12 grams/day, which represents 25-30 percent less than the ad lib-feeding, significantly reduced the incidence of intestinal tumors compared to controls. The final body weight of these rats was approximately 1/3 lower than the ad lib-fed rats, but the rats appeared healthy. This latter observation, although not entirely new, suggests a dietary approach to either the prevention or reduction of colon cancer incidence.

Project Coordination/Workshops

As an outgrowth of a workshop held in June 1983, a board of editors has been appointed to publish a quarterly newsletter for distribution to patients with hereditary forms of colorectal cancer and to their physicians. This project will be sponsored in part by the Large Bowel Cancer Project.

In April 1984, a workshop was held to discuss the topic, "Is the Marmoset an Experimental Model for the Study of Gastrointestinal Disease?" The workshop was co-sponsored by the National Cancer Institute; National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; Division of Research Resources; Oak Ridge Associated Universities; and the National Foundation for Ileitis and Colitis. The applicability of a particular species of Marmoset, Saguinus oedipus oedipus as a model for the spontaneous development of colitis and colon carcinoma was addressed by a faculty of experts. The discussion focused on how well the model simulated the human disease and its feasibility. The proceedings will be published as a monograph.

The proceedings of the workshop held in September 1982 were published in early 1984: Markers of Colonic Cell Differentiation. In Wolman and Mastromarino (Eds.): Progress in Cancer Research and Therapy. New York, Raven Press, 1984.

Pancreatic Cancer Project

Carcinogenesis and Tumorigenesis

Several studies have established that chemical damage can produce pancreatic adenomas and adenocarcinomas in experimental animals. Isolation and culture techniques for acinar and ductal cells and an *in vitro* model of pancreas carcinogenesis have been described. The effects of nitrosamines on explant cultures of human pancreas have been studied. N-nitrosobis(3-oxopropyl)amine (BOP) and N-nitrosobis (2-hydroxypropyl)amine (BHP) produce ductal hyperplasia, whereas nitrosodimethylamine (NDMA) produce malignant transformations. Under favorable conditions, NDMA is extensively produced in the human stomach. It is rapidly metabolized by the liver and is present in low concentrations in the blood of healthy individuals.

Enzymology

Analyses of enzymes and other proteins in pancreatic juice obtained from patients with pancreatic cancer show alterations in a number of proteins. Investigations are attempting to determine whether these protein abnormalities are a result of the carcinomatous process. Alkaline phosphatase (APase) and adenosine triphosphatase (ATPase) are localized in capillary endothelial cells of the normal mammalian pancreas. ATPase is also found in the endocrine and acinar cells, but not in the ductal cells. The presence of ATPase in the pancreas varies among different mammals. Digestive and lysosomal enzyme activities in hamster pancreatic juice are 10-15 times higher than in human pancreatic secretions. This increased enzyme activity may be relevant to the high susceptibility of the hamster pancreas to carcinogens.

Immunology

An important goal is to determine whether pancreatic tumors contain cancer-associated antigens. The search for new markers has revealed several which could enhance the possibility of early detection of pancreatic cancer. Workers have further characterized a pancreas-specific antigen, PaA. PaA is a secretory protein found in normal acinar cells and in the cytoplasm of ductal appearing cells of primary pancreatic adenocarcinoma. PaA may be useful as a diagnostic tool since serum levels are elevated in patients with pancreatic disease.

Tumorigenesis

Significant advances have been made in the identification of the cells of origin of pancreatic cancer. Although they are ductular in appearance, there is some evidence that pancreatic cancer cells may be acinar in origin. Human pancreatic adenocarcinomas generally have been considered ductal in origin due to the presence of tubular structures that were interpreted as arising from ductal proliferation. Through electron microscopy and wax reconstruction studies, it has been shown that the ductule-like proliferation associated with pancreatic diseases may be due to de-differentiation of acinar cells. This has led to reordering priorities from studies predominantly of duct cells toward an equal distribution of studies of ductal and acinar cells.

Quantitative estimates of the cells of origins of pancreatic cancer will help chart future research directions. The process of carcinogenesis, its dependence on chemical initiation, and the cellular and metabolic alterations that take place during the process are all areas requiring further study.

Diagnosis and Treatment

Diagnostic techniques include the development of a leukocyte adherence inhibition assay, refinement of nuclear magnetic resonance (NMR) imaging and positron emission tomography, and improvement of cytology. Therapeutic modalities requiring additional study are hyperthermia, surgery, radiation, chemotherapy, and combinations of these. New advances in immunodiagnostic techniques offer the potential for early diagnosis and treatment of pancreatic cancer. Immunodiagnostic techniques also offer the potential of monitoring treatment modalities which would lead to more rational and measured therapy.

Pancreatic adenocarcinoma has shown only a limited sensitivity to chemotherapy. Apparently, the problem is not due to factors relating to pancreatic tissue uptake of chemotherapeutic agents. The normal rat pancreas demonstrates a high uptake of adriamycin when injected intraperitoneally or intravenously. Different pancreatic tumors, however, react differently to chemotherapy. Cyclophosphamide, mitomycin C, and 5-fluorouracil are effective against the well differentiated transplantable pancreatic carcinoma. Poorly differentiated pancreatic carcinoma is markedly sensitive to adriamycin and mildly sensitive to mitomycin C.

The unique aspects of pancreatic cancer and the problems it presents have led to important theories that are being tested, but the results have not brought investigators significantly closer to the goals of prevention, early diagnosis, and effective treatment of pancreatic cancer. The histogenesis of pancreatic cancer is still perplexing because evidence for both acinar cell and ductal cell origin is being found.

Project Coordination/Workshops

The Pancreatic Cancer Project co-sponsored a grantee workshop with the American Pancreatic Association. Another workshop on nuclear magnetic imaging and spectroscopy explored the potential role of this new modality for the diagnosis of early pancreatic cancer.

Prostatic Cancer Project

Epidemiology and Etiology

Epidemiology studies have reported a risk enhancement associated with increased intake of proteins, total fat, saturated fat, oleic acid, and vitamin A during the age period of 30-49 years. The association was highly significant for vitamin A and approaches statistical significance for the other four nutrients. This study suggests a hypothesis, based on disturbance of the zinc-retinal binding protein-vitamin A access, to explain the relative risk enhancement effect of vitamin A on prostate cancer.

Laboratory studies on diet and prostatic cancer are receiving attention. Preliminary, unpublished data are consistent with the hypothesis that the growth of isolated clones of R-3327-H rat prostate tumor are responsive to high dietary fat. Other recent animal studies suggest that a 20 percent fat dietary supplement has a promotional effect on the spontaneous development of prostate cancer in germ-free Lobund-Wistar rats.

Another area receiving attention addresses the regulation of growth and androgen dependent prostate tumors through detection of mRNA for cellular oncogenes and subsequent determination of the dependence of gene expression on androgen. These studies, while only recently initiated, have established the relationship between two major secretory proteins of rat dorsal prostate, one of which has been purified and partially sequenced, paving the way for cloning of the protein and a search for cellular oncogene mRNA in androgen dependent tumors.

Detection and Diagnosis

There is continued focus on the diagnostic importance of androgens and androgen receptors in prostate tumors as indicators of potential tumor response to endocrine manipulation. Although much effort has been focused on defining biochemical parameters of predictive value akin to those widely used in planning treatment for breast cancer, the first clinical correlations have been limited to a few, but potentially significant, findings. It has been reported that the duration of response and survival following hormonal therapy is related to the number of antigen receptors present in tumor nuclei. Future advances in the receptor field and the clinical applications (both diagnostic and therapeutic) may stem from purification of specific receptors and development of monoclonal antibodies to these proteins.

The first extensive characterization of the physiochemical properties of the androgen receptor from human BPH has been reported. This receptor has been shown to be similar to receptors and other androgen responsive tissues. This may extend to prostate cancer, but has yet to be rigorously established. Other investigators are placing emphasis on improvement of receptor assay, either in terms of allowing the pathologist to visualize the compartmental (stromal versus epithelial) and intracellular (cytosolic versus nuclear) localization of the binding protein, or through means of improved specificity. Progress has been made in determining the role of prolactin in normal and malignant prostate tissue. Recent reports of the simultaneous effects (decreases) of indomethacin on prostatic prolactin binding and membrane fluidity suggest that these phenomena are interrelated and that prostaglandins are involved in the maintenance of prolactin receptors *in vivo*.

Recent studies have reported that dihydrotestosterone (DHT) levels 9
in men with advanced prostate cancer correlate with clinical response to

anti-androgen therapy. The average disease-free interval in patients with lower DHT levels (less than 2.0 ng/g) was 9.8 months compared to 24 months for patients with higher DHT levels (2.5 ng/g). Statistically, this difference is highly significant. Ultimately, such analyses of the androgenic machinery of the prostate may have widespread diagnostic, prognostic, and therapeutic applications.

Another advancement addresses the problem of histologically indeterminate cancers which elude a tissue diagnosis. Using two-dimensional electrophoresis of proteins derived from prostate, colon, and hepatocellular tumors, protein patterns of each have been identified. These patterns are sufficiently dissimilar to permit distinguishing these carcinomas.

Early detection of disease recurrence and metastatic lesions has long been a priority. A new method under current development in animal models is a polyamine based scan for metastatic prostate cancer.

A recent study has demonstrated a preferential effect of DFMO on the uptake of labelled polyamines by prostate derived tumors. This paves the way for studies on human prostate xenografts in nude mice and the use of positron emitting polyamines to image subcutaneous tumors in rats using a regular gamma camera.

Treatment

Cell division and tumor growth of prostate cancer in man are relatively slow compared to other tumors. Cytotoxic drugs are more effective against rapidly dividing tumor cells. Thus, an old hypothesis suggesting that androgen stimulation of tumor cells followed by cytotoxic therapy would be more efficacious than chemotherapy alone, has recently received renewed attention. Such an approach could involve methods to synchronize cancer cells in the cell cycle by first arresting them in the G1 phase, followed by stimulating the cells to rapidly synthesize DNA, followed by administration of chemotherapy. Properly sequenced, the increased pain sometimes associated with androgen priming could, perhaps, be countered with prior and concurrent administration of cytotoxic chemotherapy. Preliminary results have been reported to suggest that the administration of aminoglutethimide, androgen and combination chemotherapy (cyclophosphamide, 5-FU and adriamycin) may increase the response rate for Stage D prostate cancer patients over that achieved with aminogluthethimide alone.

Other modes of hormonal manipulation in clinical studies involve the use of LHRH analogs. The mode of action of novel anti-androgens is currently being assessed. Other approaches to prostatic cancer chemotherapy are being tested in animal models, and these include the use of cytotoxic steroids and steroidal derivatives which inhibit five alpha reductase activity in human and rat prostate.

Project Coordination/Workshops

On January 9-11, 1984, a conference was convened on Prostate Cancer: A Decade of Progress and New Horizons. This conference surveyed current research activities and accomplishments. In addition, planning meetings were held on May 5, 1984 to address radiotherapy needs, and on June 26-27, 1984 to address the area of prostatic carcinogenesis.

The Prostatic Cancer Newletter is published on a quarterly basis and is available to interested investigators free of charge. Through the newsletter, the scientific community is kept informed of current basic research and clinical information as well as workshops, conferences, and other related activities.

Plans

Research plans for FY 85 for the Organ Systems components include the following areas.

Several approaches have been used to coordinate the activities of investigators involved in The Bladder Cancer Project. The proceedings of the January 1983 Second National Bladder Cancer Conference were published under the title of "Advances in Bladder Cancer Research" as a supplement to the April issue of *Urology*. The Project sponsored its Tenth National Bladder Cancer Investigators' Workshop in January 1984. The diverse program provided plenary lectures, small workshops, poster sessions, and poster discussion group sessions with leading scientists providing perspectives on cellular transforming genes, endogenous and exogenous promoters, tumor heterogeneity, and the use of monoclonal antibodies as a tool to study specific tumor-associated antigens. A meeting of international clinical research leaders was held in tandem with the Investigators' Workshop to review the advances made in standardizing, conducting, and reporting results of clinical protocol investigations. These leaders began planning for an international conference on bladder cancer to be held in Europe in June 1985.

The National Bladder Cancer Project will emphasize the following areas for future study:

- Identify early events in initiation, promotion, and invasion of bladder cancer;
- Encourage broader involvement of discipline specialists in studies designed to improve our understanding of these processes;
- Delineate mechanistic steps in carcinogenesis which might provide clues for new preventive and tumor antagonistic measures;
- Develop marker systems for effective diagnosis of early lesions, particularly to distinguish characteristics between low and high-grade malignancies;
- Utilize monoclonal antibodies as a tool for the study of specific bladder cancer associated antigens;
- Develop criteria for determining optimal follow-up techniques and schedules for individuals with bladder cancer;
- Develop a system for surveillance and feedback of information to investigators conducting clinical studies;

- Sponsor a workshop on carcinoma in situ to define the entity in pathological and clinical terms.

The Breast Cancer Program will explore initiatives in the following areas:

- DNA sequence changes and/or cytogenetic abnormalities associated with breast cancer and/or with high risk for "genetic" breast cancer;
- Analyses of additional breast cancer prone families for possible linkage between susceptibility and known polymorphic chromosomal markers in addition to GPT-1;
- Assessing the frequency in the population of such a gene or genes for susceptibility;
- Investigations on possible mechanisms by which genetic susceptibility may be phenotypically expressed, including possible subtle differences in hormonal profiles and/or presence of antibodies to mouse mammary tumor virus or of certain major histocompatibility antigens;
- Further investigations on the possible etiologic relevance of viral antigens for human breast cancer in both sporadic and "familial" breast cancer;
- Confirming the value of these markers as diagnostic and/or prognostic tools in human breast cancer;
- The possible role of luteal phase defects in breast cancer risk;
- The importance of vascular and lymphatic invasion as a prognostic indicator;
- Value of prophylactic mastectomy, especially in women at high risk for breast cancer;
- The possible role of psychological trauma around the time of menarche as a predisposing factor for breast cancer;
- Possible role of the emotions and of stress in the natural history of breast cancer;
- Efficacy of new diagnostic modalities such as optical spectroscopy and NMR for early detection and diagnosis of breast cancer;
- Value of the aspiration needle biopsy as a diagnostic tool for some cases of breast cancer;
- Exploring relations between the physiological aging processes in the breast and the development of cancer;
- Investigations of possible mechanisms by which dietary components apparently enhance the development of mammary cancer;

- Exploring mechanisms by which certain dietary nutrients, particularly specific vitamins and other anti-oxidants, act as protective agents against mammary tumorigenesis;

- Risk of breast cancer in DES-treated mothers and their DES-exposed daughters.

Research plans for the Large Bowel Program for FY 85 and beyond include the following:

- Special emphasis will be placed on preventive measures, including identification of mutagens and naturally occurring or endogenously formed carcinogens.

- The role of dietary factors such as cholesterol, the various fats and fibers, and antioxidants in colon tumorigenesis will be pursued to uncover mechanisms and to resolve conflicting data.

- Cellular and phenotypic markers to identify high-risk individuals with hereditary large bowel cancer syndromes will be developed.

- Markers to identify risk for large bowel cancer other than hereditary forms will be studied.

- Cell surface structures will be investigated in an effort to determine any abnormal, exploitable characteristics for improved diagnosis or therapy.

- Factors associated with colon tumor cell heterogeneity and metastatic potential and invasiveness will be investigated.

- Cellular and biochemical properties related to growth control and metastatic potential will be identified and explored.

- High priority will be given to the development of innovative approaches to colon cancer treatment.

- Model systems will be improved to better predict the clinical responsiveness of human colon and rectal tumors.

- Colon tumor cell resistance and susceptibility to various therapeutic agents will be studied intensively.

- Collaborative efforts with existing clinical groups with an interest in colorectal cancer will be expanded.

Workshops have been planned for the following topics. A joint workshop will be held for all the Organ Systems Programs on the future of NMR scanning and spectroscopy in understanding the basic biology of tumors and the applicability of NMR to diagnosis and prognosis. The Biology and Treatment of Colorectal Cancer Metastases workshop will update the state of the art, define the important clinical questions that need to be addressed, and establish research priorities. A workshop on Carcinoma of the Large Bowel and Its Precursors will focus on the relationship of various disease states to the subsequent development of malignancy, and new screening and diagnostic techniques for colorectal cancer.

The National Pancreatic Cancer Project will conduct the following activities to further pancreatic cancer research:

- Explore tumor markers and immunology as promising approaches for detecting early stages of pancreatic cancer;
- Develop the LAI assay to the stage of clinical usefulness;
- Increase the information available on the epidemiology of pancreatic carcinoma and define which socioeconomic, environmental, and dietary factors are important;
- Develop additional methods for isolation and culture of pancreatic ductal and acinar cells;
- Develop and improve non-invasive imaging methods for detection of small tumors in this relatively inaccessible organ;
- Stimulate basic studies of pancreatic cellular and molecular physiology to lay a foundation for future research on pancreatic cancer;
- Continue studies of the histogenesis of pancreatic cancer with emphasis on both acinar and ductal cell origin;
- Continue work on the correlation between pancreatic cancer and enzyme ratios in pancreatic juice.

Specific areas of emphasis for the Prostatic Cancer Project include:

- Risk factors and chemoprevention approaches in populations at risk of prostatic cancer;
- Environmental and occupational factors in the etiology of prostatic cancer;
- Heterogeneity of normal and malignant prostatic cells;
- Endocrine alterations associated with the development of prostatic cancer;
- Growth and maintenance of normal, benign, and malignant human prostatic epithelium *in vitro*;
- Microassay techniques for measuring receptors in prostatic tissue;
- Hormone receptors, steroid levels, and enzyme profiles in normal, BPH, and cancerous prostatic tissue;
- Prostatic binding systems for substances other than hormones (polyamines, prostaglandins, drugs);

- Role of peptide hormones and other growth factors in growth regulation of normal and neoplastic prostatic epithelium;
- Oncogene(s) and genetic regulation in the development of prostatic cancer;
- Animal models for the study of induction, modulation, and prevention of prostate cancer;
- Radioisotope agents for detection and staging of metastatic prostate cancer;
- New biochemical and other markers for detection of patients with prostatic cancer;
- Non-invasive imaging techniques for the detection of prostatic cancer;
- Morphologic definition of lesions associated with, and precursor to, the development and progression of adenocarcinoma of the prostate gland;
- Relationship of human hybridoma to prostatic carcinoma.

Current priority areas are:

- Evaluation of nutritional status and nutritional intervention in advanced prostatic cancer;
- Studies of the development of resistance and tumor cell heterogeneity in prostatic cancer;
- Biology of invasiveness and metastatic spread in prostatic cancer;
- Evaluation of the significance of morphologically intact tumor cells in biopsies following radiation therapy;
- Refinement of localization techniques for external radiotherapy.

Using the task-force approach, two initiatives are planned to encourage technical and clinical research development in the areas of the application of flow cytometry in the diagnosis and treatment of bladder cancer, and the application of nuclear magnetic resonance in the diagnosis and treatment of cancer. The establishment of a network of four or five flow cytometry laboratories is proposed for carrying out collaborative studies of exfoliated bladder cancer cells. This project will channel the efforts of the best scientists in the field in the direction of developing a state-of-the-art laboratory network to serve the current needs of bladder cancer research. The intent of the proposed program is to initiate and support only inter-institutional aspects of clinical studies among flow cytometry laboratories which are already contributing to bladder cancer research. The proposed network will evolve optimum methods for identifying bladder cancer through steps of technique modification and refinement.

Flow cytometry will be evaluated for detecting tumor recurrence in bladder cancer patients who receive chemical or radiation therapy, or immunotherapy, and for monitoring symptomatic patients and high risk populations. Studies will be supported to determine the spectrum and performance of available cell markers and dyes in the flow cytometry of normal, pre-neoplastic, and neoplastic bladder cells. This work will provide for the coordinated development of new methods of cell collection, preparation, and preservation; of cell measurement and analysis; and of data analysis and processing. Reference sets of flow cytometry scattergrams relating to the various forms of bladder cancer before and during specific intravesical treatments will be established. The last area will provide for research on the flow cytometry of exfoliated neoplastic cells in urine, rather than in bladder washings. This research might move the technique of flow cytometry into the area of screening high risk populations. The end result would be the achievement of a capacity for using flow cytometry to evaluate and document tumor recurrence in studies of bladder cancer patients receiving intravesical chemo- and immunotherapy. This would reduce the need for recurrent inpatient cystoscopy in the evaluation of research results. Benefits to the bladder research field could be enormous if the goals of this project are successful. An automated technique for detection and documentation of early bladder carcinoma, recurrent bladder carcinoma, and effects of treatments on bladder tumors could bring a high level of diagnostic accuracy to urologic research facilities throughout the country.

An Operations Office will be established for organizing a network of nuclear magnetic resonance (NMR) laboratories to carry out research in the detection and treatment of cancer. The objective is to foster a network of NMR laboratories capable of carrying out collaborative studies of cancer patients in the areas of diagnosis and treatment. The network will standardize and channel research on the development of NMR methodology and will increase the quantity and quality of research being conducted with existing populations of cancer patients. Standardization of research protocols by the network will enhance the development of diagnostic formats especially designed for studies of specific types of cancer, taking advantage of research opportunities offered by existing cancer patient populations. The collaborating laboratories will evolve optimum criteria for detecting the types of cancer which are best visualized by NMR. The end result will be the achievement of a capacity for accurately monitoring symptomatic patients and for documenting and evaluating tumor recurrence in patients receiving chemical therapy, radiation therapy, or immunotherapy.

STAFF

Cancer Centers Branch:

Branch Chief:	Lucius F. Sinks, M.D.
Program Director:	Robert F. Browning, Ph.D. Margaret E. Holmes, Ph.D. Raymond A. Morrison Herbert B. Pahl, Ph.D.
Secretarial Support:	Regina Berthold Australia Jean Worsley

Organ Systems Section:

Section Chief:	Andrew Chiarodo, Ph.D.
Program Director:	Elizabeth P. Anderson, Ph.D. Vincent J. Cairoli, Ph.D. Donald E. Henson, M.D. Chester V. Piczak William E. Straile, Ph.D.
Grants Technical Assistant:	Phoebe W. Edwards
Grants Clerk:	Dorothy O. Adams Erin L. Crawford Cynthia J. Stoltz Irene H. Towns

Research Facilities Branch

OBJECTIVES

In accordance with the authorization specified in Section 410 of the National Cancer Act of 1971 (PL 92-218), the National Cancer Institute has a program which supports construction of cancer research facilities. The intent of this program is to create necessary facilities for cancer research. Facilities such as basic research laboratories, clinical research facilities, animal facilities, and associated administrative, laboratory, and service space are jointly funded. Each Federal grant dollar must be matched by equal funding from the non-Federal research institution. In all instances, the facilities proposed must be intended for expansion of existing cancer research. It is the goal of this program to upgrade research capabilities at existing cancer centers and to enable new strong multidisciplinary cancer research efforts at centers of excellence.

OVERVIEW

The National Cancer Institute's Research Facilities Program is a unique resource within the Institute. It provides facility support to the extramural programs of each of the operating Divisions by use of the construction grant mechanism. Located in the Division of Cancer Prevention and Control, the program provides research facility support for the development and operation of Cancer Center core activities as well as research activities in prevention, detection, and treatment of cancer.

In addition, the program provides technical engineering and architectural services to other NIH Institutes, particularly the National Eye Institute, in the fulfillment of facility development mandates. The Research Facilities Branch also provides support to the NCI program managers concerning alteration and renovation activities which are funded by R01s and program project grant areas.

The primary review and evaluation of construction applications is essentially scientific. Consideration is given to the following criteria: scientific merit of the proposed program(s); technical competence of the applicant institution staff; intellectual environment of the institution; and its scientific, fiscal, and administrative capabilities. Other criteria include the applicant institution's role in the National Cancer Program, promptness with which construction can be started, whether space requested is commensurate with projected program scope, space utilization, reasonable cost, and acceptable design. The applicant institution must also demonstrate its ability to satisfy the fifty percent matching fund requirement.

New cancer research programs and the provision of safe facilities for accomplishing biohazardous cancer research make construction funds an essential part of many NCI research programs. Construction support is also needed for facility expansion so that cancer scientists can work together, rather than be dispersed throughout an institution. Some programs, such as research in the use of NMR in clinical treatment, require the construction of special facilities.

The construction program continues to upgrade existing buildings for laboratories and clinical research units, some of which are biohazard containment facilities. These will minimize cross-contamination and will prevent the release of potentially cancer-causing materials into the laboratory or the surrounding community.

ACCOMPLISHMENTS

The following grants were awarded in 1984.

The University of Rochester's Cancer Center received a $500,000 grant to build a one-floor addition over their existing facility. The grant was matched by $2,300,000 from the University of Rochester. The NCI construction grant will build 5,200 square feet of new laboratories for the Immunology Research Program and 1,400 square feet of new laboratories for the Immunotherapy Research Program.

The La Jolla Cancer Research Foundation received a $300,000 grant to build a major addition to their existing research facility. The $300,000 grant was matched by $914,000 in institutional funds. The grant will be used to build new laboratories for basic research programs to study the structure and function of extracellular matrix and cell surface proteins. The new cancer research addition is 12,800 square feet.

The University of Arizona's Cancer Center received a $200,000 grant to build a major new research building. The $200,000 grant will be matched by $3,200,000 in institutional funds. The grant will provide 6,000 square feet for human tumor biology research, 1,300 square feet for cytogenetics, 1,300 square feet for clinical pharmacology, and 7,600 square feet for radiation biology research. The new University of Arizona facility will greatly improve the geographic distribution of the NCI funded cancer research centers.

PLANS

At the request of the President's Cancer Panel, a project for the evaluation of cancer facility research needs has been undertaken. The objective of this project is to identify current and future needs for cancer research facilities, including the identification of major pieces of fixed equipment. The project will produce a categorization of the research support facility needs, identify the future uses for such facilities, and develop a justification for such use. The survey will enable an accurate analysis of current national needs for construction. Several surveys have been performed over the past five years to estimate the need for cancer facility construction. All of the surveys lacked designs and controls to minimize potential bias. The current survey will build on information gathered by the past efforts, and couple this information with an improved survey design to maximize the accuracy of the data collected.

STAFF

Branch Chief:	Donald G. Fox, Ph.D.
Deputy Chief:	Kenneth A. Brow, P.E., M.E.A.
Project Engineer:	William E. Cissel, Jr.
Project Architect:	Douglas C. Dolan, R.A.
Secretarial Support:	Carmen A. Herbert Karen S. Brown

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Community Oncology and Rehabilitation Branch

OBJECTIVES

The Community Oncology and Rehabilitation Branch (CORB) is involved in many aspects of cancer patient management. The Branch supports cancer control research, linking community programs and their resources with biomedical research programs and clinical oncology expertise. Evaluation research projects and studies on the impact of social and emotional factors on the course of cancer diagnosis and treatment are encouraged within this Branch. The Branch also encourages research on the lifestyle adaptations of those individuals who have been cured of cancer or have been identified as having progressive disease. All research projects identify needs and problems associated with cancer. Research results are used to enhance patient care, utilize scarce and/or existing resources, and systematically promote more effective approaches (interventions) for providing optimum patient care in the areas of diagnosis, pre-treatment evaluation, treatment, continuing care, and rehabilitation.

OVERVIEW

CORB is organized into a Community Oncology Section and a Treatment, Rehabilitation, and Continuing Care Section.

The Community Oncology Section, which focuses on cancer treatment issues, includes:

- Community Clinical Oncology Program (CCOP),
- Cooperative Group Outreach Program (CGOP),
- Community Hospital Oncology Program (CHOP),
- Patterns of Care Studies.

The Treatment, Rehabilitation, and Continuing Care Section conducts research in the following areas:

- Strategies to increase the effectiveness of health professionals in delivering optimum care to patients and their families;
- Therapeutic regimen management;
- Supportive care studies (for both patients and families) including research on emotional and social factors, studies on home care, and approaches to better management of patients with advanced cancer;
- Pain management strategies;
- Maintenance and restoration of physical function for those disabled and impaired by cancer;
- Prosthetic and plastic reconstruction technology research.

The Programs and projects included in these Sections are described below. An integrated evaluation of these programs is described at the end of this branch report.

COMMUNITY ONCOLOGY SECTION

Community Clinical Oncology Program

Objectives

More than 80 percent of cancer patients are treated in the community. Over the past decade, increasing numbers of highly trained clinical cancer specialists experienced in clinical research and protocol care have entered community private practice and are available to extend clinical trials to community patients. Experience within several Cooperative Groups has indicated that physicians caring for cancer patients in the community can maintain high quality clinical research activities similar to those in academic centers. Evidence exists that new technology can be effectively tested and utilized by community physicians participating in clinical research activities. The Community Clinical Oncology Program (CCOP) is a major research initiative specifically intended to involve community physicians in clinical trials through participation in NCI-approved research protocols.

The objectives of the Community Clinical Oncology Program are to:

- Expedite the transfer of advanced cancer care technology to community application;
- Secure the benefits of therapeutic research care for patients in their own communities;
- Increase accrual to high priority protocols, thus reducing the time necessary to answer critical research questions;
- Use research protocols as educational tools to help oncologists in community practice maintain state-of-the-art cancer care;
- Create a network for controlled distribution of experimental cancer agents;
- Create a resource for implementing cancer control and prevention research initiatives of the NCI.

Overview

Through the CCOP the opportunity exists to increase patient accrual to clinical trials, and thereby answer research treatment questions more rapidly, and, at the same time, provide the benefits of clinical investigations to community oncologists. It is expected that what is learned from direct participation in clinical trials can and will be extended to other cancer patients in community settings.

The CCOP can also be considered as one of the best continuing medical education programs yet devised. Through the CCOP, skilled medical investigators will learn through experience while continuing their involvement with research bases. This exposure to state-of-the-art cancer care will ultimately benefit most community patients. Clinical trials designed to reduce morbidity and mortality from cancer are also a form of cancer control. CCOP is a comparative trial (Phase III) in cancer control research and is involved in efficacy (Phase II) and treatment comparisons (Phase III) in cancer treatment research.

Each Community Clinical Oncology Program is required to enter or refer patients into clinical trials designated as high priority by a research base currently conducting NCI-approved clinical research protocols. These research bases are responsible for protocol development and data collection and analysis. Each CCOP may affiliate with up to five research bases. The 62 currently funded CCOPs are affiliated with 14 Cooperative Groups and 17 Cancer Centers. Participants are encouraged to enter on protocol patients with early stage disease with common cancers and to enter on protocol or refer to research bases patients with uncommon cancers.

The three-year awards for the CCOPs are in the form of cooperative agreements, the predominant funding mechanism for the NCI clinical trials programs. (Cooperative agreements are essentially a partnership between the government and the recipients of the awards.) The cooperative agreement mechanism will ensure consistency and quality control procedures in the application of clinical trials in the community setting. This mechanism is also used to reimburse the research bases for CCOP data management costs.

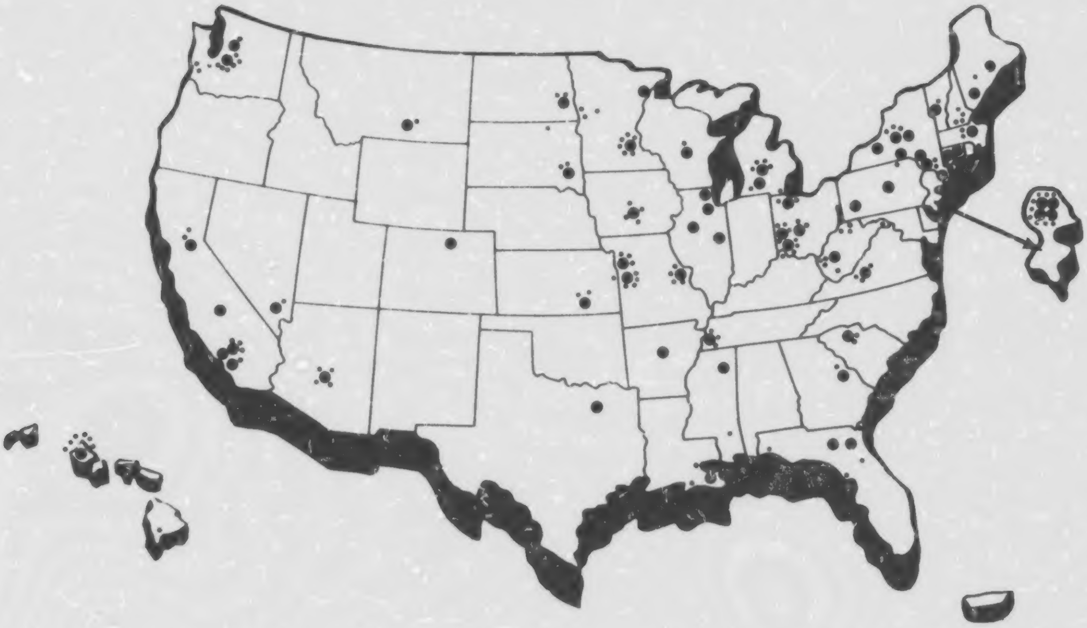
Plans and Accomplishments

In September 1983, awards were made to 62 CCOPs in 34 states. These CCOPs include 189 hospitals, 63 physicians' offices, and 21 group practices (see Figure 10). A total of 1,220 physicians participate in clinical trials through this program, and an estimated 6,000 patients per year will be entered on research protocols. Accomplishments in FY 84 include:

- Orientation meeting for CCOP research base representatives;
- Orientation meeting for all CCOP principal investigators and data managers;
- Establishment of a CCOP Advisory Group, consisting of seven CCOP principal investigators, one nurse/data manager, and one hospital administrator, which met three times in FY 84;
- Preparation and dissemination of five Information Memoranda describing CCOP progress to all participants and others interested in the program;
- Establishment of a computerized data base for CCOP administrative information and patient log data;

FIGURE 10

Location of CCOPS and Hospital Components



- Site visits by program staff to all CCOPs during the first year award period;

- Accrual of more than 4,000 patients to NCI-approved clinical trials between September 1, 1983 and August 31, 1984.

Progress of the CCOPs will be reviewed by program staff in July 1984, with consideration given to reports from the CCOPs, research bases, and site visits. Preliminary information suggests that a very high percentage of the total number of CCOPs are accruing patients at, or better than, the rate predicted. Although some CCOPs may be placed on probation, and some may be terminated after the first year, it is anticipated that most awards will be continued.

It is expected that the CCOPs will provide a focal point for introduction of other programs in the community, such as large-scale clinical trials screening programs or prevention trials.

Cooperative Group Outreach Program

Overview

The Cooperative Group Outreach Program (CGOP) seeks to upgrade the skills of community physicians and other health professionals in the management of cancer patients, and to increase the number of these patients receiving the best available care. Its ultimate goal is to reduce cancer morbidity in the community.

The objectives of the CGOP are to:

- Strengthen and enlarge the affiliated hospital programs of the Cooperative Groups to increase the participation of community health professionals in well-defined and monitored protocols for the management of cancer patients,

- Provide support services to community physicians to maintain a high standard of patient care and data collection,

- Institute quality control of patient management by the analysis of treatment data to ensure high standards of care for patients entered on treatment protocols,

- Provide continuing educational activities for community health professionals.

Plans and Accomplishments

This program currently funds six Clinical Cooperative Groups with a total annual budget of approximately $4 million. These groups are:

- Childrens Cancer Study Group,
- Eastern Cooperative Oncology Group,

- Northern California Oncology Group,
- National Surgical Adjuvant Breast Project,
- Radiation Therapy Oncology Group,
- Southwest Oncology Group.

The locations of the outreach program affiliates are shown in Figure 11.

In October 1983, the DCPC Board of Scientific Counselors approved a staff recommendation to continue the Cooperative Group Outreach Program for three years. New awards will be made as Cooperative Agreements. Accomplishments so far include:

- Issuance in February 1984 of an RFA to continue the program,
- Receipt in March 1984 of 13 letters of intent to respond to the RFA,
- Receipt of 12 applications in May 1984.

The NCI expects to make awards in April 1985 after peer review of the applications in the fall of 1984.

Community Hospital Oncology Program

Overview

The Community Hospital Oncology Program (CHOP), a cancer control effort aimed at physicians practicing in the community setting, was designed to improve the care of cancer patients through the development and implementation of multidisciplinary patient management guidelines, nursing and rehabilitation guidelines, educational programs, supportive care, and continuing care activities in the community. Under this model, community cancer care providers and community hospitals without major affiliations with comprehensive or university cancer centers planned and developed a program which provided guidelines for comprehensive "state-of-the-art" medical care, supportive care, and educational opportunities for patients, family members, and health care professionals.

The objectives of the Community Hospital Oncology Program were to:

- Ensure that appropriate and complete pretreatment evaluation and staging of newly diagnosed cancer patients were available in the community;

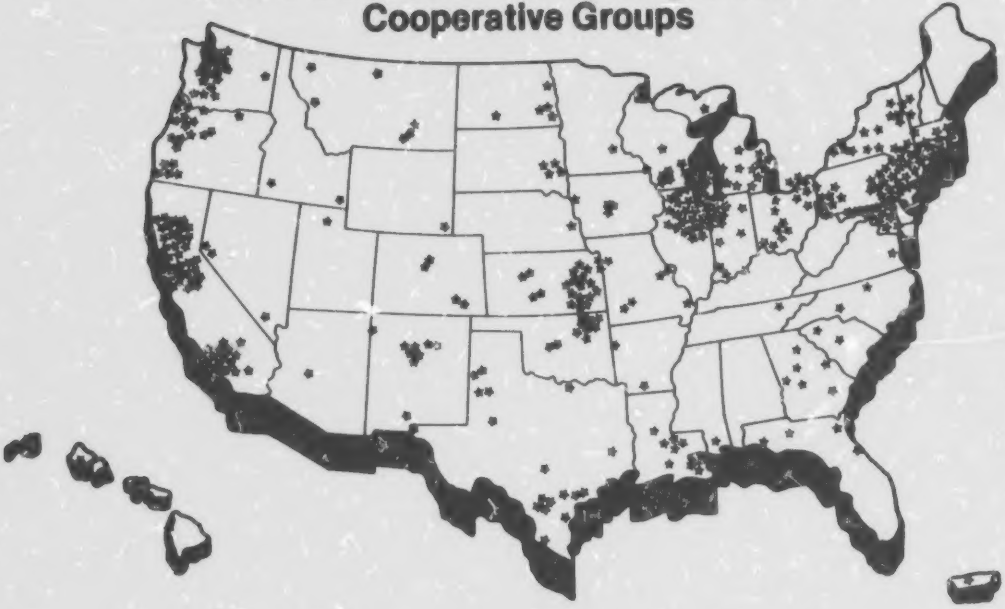
- Ensure that multidisciplinary recommendations were incorporated into patient management decisions;

- Ensure that appropriate specialized treatment protocols were available in the community and that referrals to specialized centers were facilitated for cancer patients needing such care;

- Ensure that cancer nursing procedures were of the highest standards and carried out under the advice and guidance of trained oncology nurses;

FIGURE 11

Location of Organizations Participating in the Cancer Control Outreach Programs of the Cooperative Groups



- Ensure that necessary cancer rehabilitative and appropriate supportive care resources in the community were available and utilized;

- Ensure that the terminally ill received the benefits of modern pain and symptom management in an atmosphere that emphasized the quality of survival and death with dignity;

- Ensure that up-to-date cancer management information was continuously made available to physicians, nurses, and other health care personnel;

- Ensure that a cancer data management system was in place that permitted monitoring of program effectiveness, documentation of program accomplishments, assessment of community cancer care practices, and patient outcome status;

- Ensure that the community cancer care program would continue after Federal funding ceased.

Plans and Accomplishments

Following an 18 month planning phase, 17 CHOPs entered a two-year implementation phase which was completed in FY 84. Site-specific committees at each CHOP, composed of community physicians representing multiple disciplines and other health care providers, participated in the development of "state-of-the-art" patient management guidelines (PMGs) and developed data management systems to monitor cancer care. Patient management guidelines were distributed to hospital and community physicians and to allied health professionals. Tumor boards, tumor conferences, seminars, and other continuing educational forums were utilized to increase the awareness and involvement of health care professionals in implementing cancer care through the appropriate use of patient management guidelines and clinical staging. Health care and community resources were identified to strengthen and improve the available support services responding to continuing care needs of cancer patients.

Although there was great diversity in the CHOP communities, the implementation of this cancer control program stimulated the following changes in some of the CHOPs:

- An improvement in cancer care as a result of health care professionals participating in the educational process of developing and applying patient management guidelines;

- An increase over time in the percentage of cancer patients managed and staged according to PMGs for site-specific diseases (e.g., breast, colon);

- An increase in cancer educational programs for health care providers, patients, family members, and community participants;

- An improvement in the health care provider's identification of cancer related problems in the areas of rehabilitation and nutrition;

- An improvement in the coordination of community resources and supportive services created to provide for the needs of cancer patients;

- The development and distribution of community resource manuals of support services and programs available to cancer patients;

- The development of hospice programs;

- The successful application and approval of 11 CHOPs for COOP funding which will provide clinical research protocols to community patients;

- An increase in nursing oncology educational activities and chemotherapy certification programs;

- The development of patient and family support groups and bereavement groups;

- A greater involvement of community cancer care providers in local and State agencies having a major impact on policy decisions affecting cancer patients.

Initial results of the local evaluations show that compliance to PMGs varied from CHOP to CHOP due to variations in guideline definitions and non-uniform measurement of what constitutes compliance. Completion of staging forms by physicians gradually improved in some CHOPs after extensive continuing educational efforts. The initial fear of many CHOPs that the attachment of PMGs to hospital records would create medico-legal problems was not realized. The local evaluation was complicated by the diversity and complexity of PMGs initially developed. Feedback from the research process was minimal. However, a few CHOPs were able to incorporate the results of the local evaluation activity to strengthen their programs.

The combined CHOP Pilot Study of Patterns of Care was completed by the Statistical Analysis and Quality Control Center (SAQC) of the Fred Hutchinson Cancer Center during FY 84. The major objective of the pilot study was to determine the feasibility of using patterns of care parameters to track cancer patient care management practices. Three signal diseases were selected for the pilot study--breast, colon, and oat cell lung cancers. Preliminary analysis of the pilot study showed that certain data elements were not available in hospital records, and some parameters of cancer care were less useful in differentiating and characterizing patient management practices in the areas of pretreatment evaluation, staging, management, and follow-up. This information has been used to design the Patterns of Care component of the Integrated Evaluation of Community Cancer Care Programs.

Several of the CHOPs will be able to continue elements of the CHOP model through support from outside sources such as third party carriers (e.g., Blue Cross/Blue Shield in the Toledo CHOP), and foundation grants (the Kalamazoo

CHOP). In some areas, CHOP elements and activities have been integrated and institutionalized into existing hospital oncology programs.

Patterns of Care Studies

Patterns of Care for Elderly Cancer Patients

To encourage studies that would contribute to our understanding of the management of cancer in the elderly, the National Cancer Institute directed a research effort in FY 83 to focus on the older cancer patient. Since cancer is primarily a disease which occurs in the older-aged segment of the population (i.e., approximately 50 percent of all cancers occur in persons 65 years and older; close to 60 percent of all cancer deaths occur after 65 years of age), the risk of developing cancer increases rapidly with each decade of life. Unfortunately, little is known about how the problems of old age affect cancer work-up, treatment, and care.

Not only does cancer affect the older age group in our society disproportionately, but the nation's number of older persons is gradually increasing and will constitute a larger percentage of the population in the future. In 1900, the over 65 years of age group numbered 3.1 million persons and represented only 4.1 percent of the entire population. By 1975, this same age group had 22.4 million persons and represented 10 percent of the population; estimates for the year 2000 predict a rise to 33.2 million persons making up almost 12 percent of the U.S. population. By 2030, possibly the peak year for the overall growth of the population, there will be approximately 55 million persons 65 years or older in the U.S. Trends in recent years demonstrating decreases in deaths from cardiovascular disease will increase the number of the elderly at risk of developing cancer. Clearly, within the context of the U.S. health care system, there will be more old people who require cancer care.

When cancer is linked with the chronic disabling conditions acquired over the course of a lifetime, the aftermath of previous illnesses, and the effects of both normal and pathological processes of aging, providing treatment and care to elderly cancer patients can be extremely complicated. The frailty of older-aged persons; their other health difficulties and chronic disabilities; and social, psychological, and economic handicaps all combine and interact to complicate the process even more. The dearth of data makes it impossible to provide definitive answers to the many questions which arise about the impact of old age on cancer patient management.

A Request for Applications (RFA) entitled Patterns of Care for Elderly Cancer Patients: Implications for Cancer Control, was designed to stimulate the fields of oncology, gerontology, and other relevant disciplines and professions to conduct multidisciplinary research about cancer treatment and care of the older-aged population. The research initiative was issued in consultation with the National Institute on Aging (NIA). Applications were sought on the natural history of cancer in the elderly, treatment patterns, the interaction of the normal and/or pathophysiological processes of aging and cancer, the overlap of intercurrent disease with cancer, and the extent to which interdisciplinary approaches may foster coordinated application of special skills for optimal cancer care for the elderly. The assessment of the patterns of care (i.e., the diagnosis, work-up, staging, and treatment) for evaluation of elderly cancer patients requires an adequate database.

Eleven awards have now been made to investigators in FY 84. The NCI is supporting nine projects; the NIA is supporting two projects. Brief descriptions of the studies are provided below.

Researchers will examine the efficacy and toxicity of chemotherapy as well as patterns of care and incidence of co-morbidity in elderly cancer patients. Existing Eastern Cooperative Oncology Group (ECOG) databases will be utilized. Specific problems associated with chemotherapy toxicity, the incidence of co-morbid disease, and the extent to which elderly patients are treated on research protocols will be addressed.

An analysis of the relationships between age and the diagnosis and treatment of cancer will be performed using five data sets to determine whether age should be considered an important independent prognostic factor in management decisions for breast cancer, prostate cancer, and melanoma.

Existing data will be reviewed to identify variations in medical care of the aged and the probable causes for variations from patterns of care for younger patients. Data will first be analyzed from the Los Angeles County Cancer Surveillance Program, an incidence registry of all new cases of cancer for all residents of the Los Angeles County. Extent of disease at diagnosis, the presenting syndromes, and the durations of symptoms prior to diagnosis will be compared for three tumor sites (breast, prostate, and colorectal cancers) and for three age groups (50-65, 66-75, and 76 plus).

Researchers will assess the frequency of cancer symptoms in a representative sample of older persons, the response of older persons to those symptoms, and the role of the individual's support network in those responses. The study will capitalize on an existing national sample of older persons drawn for the 1980 study, "Support of the Elderly: Family/Friends/Professionals," and involve telephone interviews of 718 principal respondents from the original study and an additional telephone interview with the network member of those respondents reporting symptoms within the last four years that could be associated with cancer.

A prospective study of 800 elderly patients with lung, breast, or colorectal cancer will be conducted where age, performance status, medical management, and psychosocial, emotional, and economic factors are the parameters of interest. Subgroups of patients will be interviewed during the 12 month treatment period to determine response to the treatments and to management decisions. Physician and patient questionnaires will be administered at the time of entry to the study. Further information will be obtained from the patient's clinical record and a follow-up patient interview at 12 months. Three hundred randomly selected patients will undergo more intensive study. Information will be collected regarding physician attitudes toward the aged cancer patient and how these attitudes affect the treatment choice.

Cancer diagnosis, treatment, and survival in the elderly population of New Mexico will be examined to identify remediable deficiencies in the sequence of events from onset of cancer symptoms to diagnosis and treatment by the health care system. The analysis--directed primarily at the effects of age on stage at diagnosis, treatment, and survival--will involve approximately

40,000 cases diagnosed in a population of New Mexicans and Native Americans living in Arizona during 1969-1982. A questionnaire on knowledge and attitudes about the aging process will also be administered to a sample of physicians to correlate responses with actual practice, as documented in the New Mexico Tumor Registry.

The social support of patients diagnosed with acute leukemia and small cell carcinoma of the lung will be characterized at the time of initial treatment and subsequently, to determine if such supports are related to treatment, toxicity, or treatment outcome. Patients being treated at the University of Maryland Cancer Center for acute leukemia or small cell lung cancer will comprise the study sample.

Researchers will identify health care utilization patterns associated with a diagnosis of cervical cancer among elderly women as compared to women in the middle years to ascertain how widespread these utilization patterns are in the two populations. Additionally, researchers will investigate women's knowledge and behavior relating to early detection practices. Lastly, they will study the extent to which providers' knowledge, attitudes, and practices concerning cervical cancer detection for the elderly are consistent with, or influence, utilization and detection patterns reported by women. Implications for intervention techniques (provider- and patient-oriented) to improve early detection of cervical cancer among the elderly will be examined.

Investigators will study altered drug metabolism and disposition as a potential explanation for the enhanced toxicity and decreased complete remission rate observed in elderly patients being treated for acute nonlymphocytic leukemia and small cell lung cancers. Prior to treatment with antineoplastic chemotherapy, patients will have their hepatic and renal drug metabolizing and excretory status assessed with liver function tests, indocyanine green clearance, antipyrine clearance, and creatinine clearance. Pharmacokinetics and metabolism of the antineoplastic agents administered to each patient will be assessed. Data will be analyzed for age-related alterations in renal and hepatic drug handling status, relationships between hepatic and renal function and alterations in each antineoplastic agent's pharmacokinetics and metabolism, and several other drug interaction effects.

The role of age and various behavior factors in determining appropriate patterns of care will be studied. Reasons for the differences in survival rates between young and old female rectal cancer patients will be sought. This study will examine a sample of New York City white female patients, 45 years of age and older, with cancers of the breast or rectum, to determine the effects of age, socio-economic status, and site of disease on pre-treatment choices, treatment choices, and follow-up care offered by the physician and chosen by the patient. Identified patients and a support person named by each will be interviewed, and clinical data will be obtained from the patients' medical records and their physicians.

Two studies that focus on the management of breast cancer in elderly women and their social and psychological adjustment to the disease will be conducted. Investigators will examine the influence of patterns of primary and secondary treatment upon health and psychological functioning,

medical conditions that influence management, and patients' social support systems and their effects on adjustment. Women who were screened as part of the Breast Cancer Detection Demonstration Project, half of whom developed breast cancer and half of whom did not, will be assessed. In addition, a longitudinal study that looks at adjustment of newly diagnosed cancer patients will be conducted.

Patterns of Care Study in Radiation Therapy

The American College of Radiology is entering its tenth year of systematically assessing national patterns of care in radiation therapy. It has documented the changes in the structure, process, and outcome of radiation therapy since 1973. During FY 84, a fourth and final Facilities Master List was completed which forms a directory of megavoltage facilities in the U.S. operational as of January 1, 1983. This directory which documents the change in structure of radiation therapy practice since 1973, will be used to select the sites for the final process survey. This survey will be innovative in that it will include a study of palliative care in four areas: relief of pain, relief of superior vena cava obstruction, epidural spinal cord compression, and brain metastases. In addition, the survey will include a national study of five curative sites: cervix, prostate, larynx, Hodgkin's disease, and breast. This is the first time the Patterns of Care Study will conduct a survey on the role of primary radiation therapy in the curative treatment of early stage breast cancer.

This final survey will provide data on the most current practices in radiation therapy and the variations that may exist by geographic region and type of facility. It will provide the critical third point in the process/outcome surveys (1973 and 1978) and a firm basis on which to build a stable quality assurance program for individual facilities sponsored by the American College of Radiology.

TREATMENT, REHABILITATION, AND CONTINUING CARE SECTION

Marked improvement in survival from cancer, the result of successful research over the past 15-20 years, means that larger numbers of cancer patients can look forward to longer lives and for some probable cure. The need for stressing treatment, rehabilitation, and continuing care problems of cancer patients has never been so essential as it is now within the exciting context of increasing cures and prolonged disease-free survival. The goal set for the year 2000 is realistic and provides an additional stimulus for research aimed at improving cancer care.

Over five million persons living today have had cancer. Three million of these persons had a diagnosis of cancer five or more years ago. As treatment for cancer becomes more effective, there will be more "cured" cancer patients, but not all can return to pre-illness activity. Research efforts must be encouraged to reduce cancer morbidity, that is, the untoward physical, social, and emotional consequences of the disease. The goal is to improve the quality of life for persons who have (or had) cancer by applying existing knowledge and promoting research to acquire new knowledge. Problems accompanying the diagnosis and treatment of cancer range from the insidious to major interruptions in life style which impair physical and social functioning.

Research in continuing care and rehabilitation aims to reduce cancer morbidity by conducting comparative studies and evaluable demonstration projects on effective techniques, procedures, and protocols that have specific applicability to physical, cosmetic, functional, social, and psychological problems related to cancer. During FY 84, staff reviewed information obtained from previous grants and contracts supported by the Division. In addition, workshops on specific areas with high potential for treatment, rehabilitation, and continuing care research were held (e.g., head and neck cancer, cancer survivorship). In July 1984, a workshop on cancer nursing research priorities was held to focus on specific oncology nursing interventions as they relate to cancer patient management and the full spectrum of activities in CORB.

A descriptive follow-up study of NCI's Training Program for Maxillofacial Prosthodontists and Maxillofacial Dental Technicians was conducted in FY 84. The study examined the dental practice activities of persons who received NCI-sponsored training in the treatment and rehabilitation of patients with head and neck cancer.

In the three meetings of the DCPC Board of Scientific Counselors' (BSC) Subcommittee for Centers and Community Oncology held within the past year, the advice of Board members was sought on program development and evolving concepts for the treatment, rehabilitation, and continuing care programs area. The combination of the subcommittee's advice, workshops, prospective studies and staff assessment activities evaluating previously awarded studies are providing the knowledge base for program planning.

General recommendations for research include:

- Emphasize selected aspects of cancer pain and management therapy which include the transfer and utilization of optimum pain management techniques, pharmacologic studies, adherence to medical regimens, emotional support, and pain prevention;

- Transfer the technology of pain management to nurses, pharmacists, and physicians;

- Identify and test interventions to reduce morbidity and the consequences of cancer for patients and their families on social, psychological, physical, and economic dimensions;

- Disseminate the research findings on the influence of old age on cancer patient work-up, treatment, and care in a rapid manner;

- Target selected cancer sites--head and neck, breast, and childhood cancers--for quality of life and rehabilitation efforts;

- Investigate the development and design of effective ways to follow up cancer survivors to improve the quality of life for cancer patients and their families;

- Investigate ways to meet the special problems that cancer patients face by conducting research on their concrete needs and efficacious solutions to these problems;

- Follow up on findings from recent research conducted on cancer of the breast, bladder, large bowel, prostate, and pancreas, and issue focused research initiatives incorporating rehabilitation and continuing care components;

- Initiate research on methods which improve patient access to state-of-the-art cancer care and treatment.

Summaries of Rehabilitation and Continuing Care Workshops

Head and Neck Cancer: The Integration of Treatment and Rehabilitation

The purpose of this workshop, held in January 1984, and sponsored by the Community Oncology and Rehabilitation Branch, was to review past research directions and set new goals, where appropriate. Approximately 30 papers were presented covering such topics as the cosmetic and functional consequences of neck dissections, reconstructive procedures, and the relationships among treatment, speech, voice, and swallowing. Other topics addressed were the site of optimal care for the head and neck cancer patient (community or center) and a variety of patient-specific issues (e.g., compliance, pain, etc.).

As discussed at the workshop, the goal of integrating treatment and rehabilitation is to prevent or minimize the physical (cosmetic or functional) disability and the emotional sequelae commonly associated with head and neck cancer and its treatment. Two broad approaches to this goal were considered: programs which involve direct monitoring of treatment and programs that involve measuring the consequence of treatment and then modifying future treatment regimens (a two-step approach). Research designed to facilitate both types of activities was proposed at the workshop.

Specific research activities proposed by meeting participants included:

- Development and implementation of standardized measures of speech, voice, and swallowing; their integration into clinical protocols; and their application in clinical practice to assure balanced interpretation of treatment and rehabilitation results;

- Development and evaluation of multidisciplinary teams and/or centers to care for the head and neck patient;

- Development of new prosthetic materials (materials that resist heat and sun and retain their shape);

- Performing clinical trials to compare the outcomes relative to radical and conservative neck dissections.

Suggestions for additional areas of study included:

- Normal physiology of swallowing, leading to computer simulation of the swallowing act;
- Physiological basis and pathological consequences of imperceptible aspiration with long-term follow-up;
- Pain management;
- Impact of the behavior of the head and neck patient (non-compliance, drinking, and smoking) on the clinical course and outcome of treatment;
- Effects of Diagnosis Related Groups (DRGs) and the prospective payment system on referral patterns and patterns of care.

Workshop: Focus on Cancer Survivors

DCPC and the Division of Cancer Treatment (DCT) cosponsored a workshop in February 1984 to discuss salient cancer survivor issues and concerns for cancer control research in treatment, continuing care, and rehabilitation. The purpose of the workshop was to provide suggestions to the NCI staff for research to develop information on the problems of those who survive cancer, ways to offset the problems, and methods to improve the feedback to the oncologists delivering cancer care and therapy.

Three problem areas were addressed in the meeting under the pediatric oncology rubric: complications of therapy which affect the former patient's education and development, health education and communication for patients and families and among health professionals, and methodological and medical concerns. The workshop discussion also considered adult "cured" cancer patients' problems, a research area less well described or documented because of less successful treatment and the variety of problems faced.

Retrospective follow-up studies of children are of limited use, so prospective studies are needed to define the incidence and impact of problems cancer creates for successfully treated children as they enter adolescence and adulthood. In addition, a definition of what constitutes survivorship must be formulated.

Basic data should be obtained on:

- School performance (beyond that which is measured by attendance records and psychometric test results) and intellectual functioning (e.g., learning deficits);
- Ways to educate teachers about the disease to facilitate the child's re-entry into the day-to-day school routine with peers;
- Subsequent medical problems;

- Second malignancies;
- Physical growth and anatomical development, abnormalities, growth curves, vital organ failure;
- Level of self-esteem and/or emotional adjustment;
- Financial burden of the illness and its long-term effects on the family;
- Sequelae from long-term chemotherapy (e.g., second cancers, growth problems, sterility);
- Effect of the cancer on siblings and the family in general;
- Parent and child comprehension about the illness and what to expect in the future;
- Ways to educate the medical community to the functional difficulties that cancer survivors may experience;
- Ways to train nurses to look for late effects.

With regard to follow-up of adults, there are many aspects of survivorship in need of study. These concern the extent or severity of problems related to employability, insurance discrimination, emotional adjustment, or functional impairment. The heterogeneity of this group, however, precludes application of conventional research strategies. In this context, the following questions were raised:

- What is the best way to follow survivors?
- What tests should be ordered?
- How should questions be asked?
- What tools of measurement should be employed?
- How should quality of life be defined (e.g., functionally, socially, psychologically, by achievements)? What levels of function are acceptable?
- How does one take into account the variety of responses patients may give to questions about quality of life (e.g., two patients may describe identical situations which one sees as problematic and another does not)?

Research Initiatives

Continuing Care Research: Identifying and Reducing Obstacles for Patients with Cancer

The CCO Program is developing a research initiative which addresses the continuing care needs of patients with cancer. In the past, patient need assessments and surveys of patient demand for specific services have indicated that continuity of cancer care is, at times, inefficient or ineffective. The administrative, economic, and activities of daily living problems faced by cancer patients vary greatly, and health care delivery systems are not always equipped to respond appropriately. Local resources and expertise may be limited or, although present, may be inaccessible to patients and their families because of insufficient planning or an incomplete assessment of the critical factors necessary for workable service delivery.

To correct this perceived shortcoming in current cancer care, research will be encouraged to: (1) develop prospective and accurate data detailing the incidence of resolved and unresolved practical problems facing cancer patients; (2) document and characterize existing and/or potential solutions; and (3) use existing resources to develop or improve upon systematic interventions to resolve the identified problems.

The purpose of the research is to more adequately estimate the magnitude of the concrete needs of cancer patients and to identify generalizable interventions designed to meet those needs.

Evaluation of Outreach Consultation through Tumor Conferences

One mechanism for the management of cancer patients currently in widespread use is the hospital tumor board, or tumor conference. Such a mechanism is required for accreditation by the American College of Surgeons (ACOS). Over 1,000 hospitals currently have ACOS-approved cancer programs with tumor boards, while it is estimated that approximately twice this number host regular meetings regardless of accreditation status.

The impact of consultation through the tumor board process has not been evaluated, despite the fact that tumor boards appear to be a consistent avenue for physician education and the dissemination of information relating to the latest advances in cancer treatment. Education and information transfer are closely linked to the National Cancer Institute's mandate for cancer control. Characterization of tumor boards, which differ widely in form and style, and some understanding of their impact on patient management can greatly aid the NCI's cancer control efforts. Therefore, a two-part study of tumor boards will be undertaken within the Community Oncology and Rehabilitation Branch. Initially, descriptive data characterizing the consultative process in tumor boards located in community cancer programs, university hospitals, and Cancer Centers will be collected. Subsequently, an evaluation of concordance between recommendations presented at such conferences and actual patient management techniques will be assessed to examine the extent and nature of tumor conference influence.

Follow-up Study of Maxillofacial Prosthodontists and Maxillofacial Dental Technicians

A descriptive follow-up study of the NCI's Training Program for Maxillofacial Prosthodontists and Maxillofacial Dental Technicians was completed in FY 84. The program, active from 1973 to 1982, used a competitive contract mechanism to provide a total of $3.8 million in training and development funds to seven institutions in order to help meet a perceived need for special dental expertise in the field of head and neck cancer rehabilitation. The intention of the study was to look at the strengths and weaknesses of the program and to develop a descriptive profile of the NCI-sponsored trainees.

The follow-up study revealed that NCI resources helped sponsor the training of a total of 62 maxillofacial prosthodontists and 60 maxillofacial dental technicians. It was learned that the main professional settings of most of the prosthodontic trainees who completed this NCI-sponsored training program, in descending order of frequency, are private practice, dental schools, and hospitals. The study also revealed a number of obstacles limiting the maxillofacial prosthodontic rehabilitation efforts of these dental specialists. Obstacles include limited recognition of the role of the maxillofacial prosthodontist by the surgical community and relatively limited or inadequate third party reimbursements for professional services.

The NCI training program helped to develop and strengthen the maxillofacial training programs at the seven participating institutions. A permanent increase in the number of residency training positions and staff positions occurred when financial support was identified after the NCI funding ended. Other changes included increases in patient treatment capacity and the establishment of wider patient referral networks.

The program appears to have met the objective of the original RFP, which was to provide for the training of additional maxillofacial prosthodontists and maxillofacial dental technicians. Poor assessment of the number of trainees needed and their probable acceptance by the maxillofacial surgical community resulted in a larger program than was necessary. Benefits may be derived from training additional maxillofacial prosthodontists, but until their services are sought and supported to a greater extent, there is limited need for such training efforts.

INTEGRATED EVALUATION OF COMMUNITY CANCER CARE PROGRAMS

During FY 84, considerable progress was made on the integrated evaluation of community cancer care programs. The aim of this project is to evaluate the Community Hospital Oncology Program, the Cooperative Group Outreach Program, and the Community Clinical Oncology Program and thereby: (1) provide a basis for future policy decisions regarding community cancer programs; and (2) gain an understanding of the mechanisms for information diffusion in a community setting.

The Statistical Analysis and Quality Control Center at the Fred Hutchinson Cancer Research Center was awarded a contract to design and implement the evaluation. The principal investigator is Polly Feigl, Ph.D. An oversight working group provides assistance in planning and design and advises the NCI on the progress of the evaluation. The group has a wide range of expertise including medical, surgical, and radiation oncology; biostatistics; organizational theory; and health policy and administration. A list of members and their affiliations follows this page.

The initial phase of the project involved identifying specific research questions and the detailed design to employ to obtain their answers. Four research questions were developed:

- Is there an increase in participation in clinical research protocols as a result of the programs?
- Are there changes in patterns of cancer patient management as a result of the programs?
- Are there changes in the health care systems where programs exist?
- What are the characteristics of a successful community cancer program?

The detailed design of the evaluation uses a multi-tiered approach which includes analyzing descriptive data; examining patterns of cancer care for breast, oat-cell lung, and colorectal patients before and during the programs; and conducting in-depth organizational studies and a physician survey early and late in the programs. Control programs (CCOP applicants that were approved but not funded) have been included in each tier to strengthen the overall design and analysis of the study.

The evaluation, scheduled for completion in three years, will provide critical information for the design of future community cancer programs. A substantial amount of funding for the evaluation has been received from one percent evaluation set aside funds from the Assistant Secretary for Health.

Community Cancer Care Evaluation

ADVISORY COMMITTEE MEMBERS

Chairman: Arvin Glicksman, M.D.
Chairman, Department of Radiation Oncology
Brown University
Rhode Island Hospital
Providence, Rhode Island

Gerald E. Hanks, M.D.
Radiation Oncology Center
Sutter Community Hospitals
Sacramento, California

Paul F. Engstrom, M.D.
Director, Department of Medical Oncology
Fox Chase Cancer Center
Philadelphia, Pennsylvania

John Horton, M.B., Ch.B.
Head, Division of Oncology
Albany Medical College
Albany, New York

Charles Spurr, M.D.
Professor of Medicine
Bowman Gray School of Medicine
Winston-Salem, North Carolina

Norman Wolmark, M.D.
Assistant Professor of Surgery
University of Pittsburgh
School of Medicine
Pittsburgh, Pennsylvania

Dennis Gillings, Ph.D.
Professor of Biostatistics
University of North Carolina
Chapel Hill, North Carolina

Ann L. Greer, Ph.D.
Associate Professor, Sociology
University of Wisconsin
Milwaukee, Wisconsin

Roger S. Foster, Jr., M.D.
Professor of Surgery
University of Vermont
School of Medicine
Burlington, Vermont

Richard Scott, Ph.D.
Professor of Sociology
Stanford University
Palo Alto, California

Richard Warnecke, Ph.D.
Associate Director for Cancer Control
Illinois Cancer Council
Chicago, Illinois

Arnold Kaluzny, Ph.D.
Professor, Health Policy and Administration
University of North Carolina
School of Public Health
Chapel Hill, North Carolina

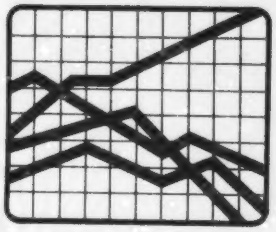
Jay Goldman, D.Sc.
Chairman, Department of Industrial Engineering
University of Missouri
Columbia, Missouri

Colin Begg, Ph.D.
Division of Biostatistics
Dana-Farber Cancer Center
Boston, Massachusetts

STAFF

Acting Branch Chief:	Jerome W. Yates, M.D., M.P.H.
Evaluation Specialist:	Leslie G. Ford, M.D.
Program Analyst:	Wilma H. Dunlap
Program Director:	Robert W. Frelick, M.D. Carrie P. Hunter, M.D. Dorothy K. Macfarlane, M.D.
Statistical Assistant:	Clarice Radabaugh
Secretarial Support:	Cheryl Fisher Donna L. Gansel Constance O. Kay Nancy R. Kesteven Felicia R. March Denetrices A. Ramsey Linda S. Wong

Cancer Control Science Program



Associate Director's Report

The Cancer Control Science Program (CCSP) supports an integrated approach to cancer control research and applications. The Program supports projects to identify opportunities for, and facilitate the widespread application of, effective cancer control interventions. This is accomplished through a systematic and orderly sequence of research phases to establish the hypotheses necessary to reduce cancer incidence, morbidity, and mortality; develop the methods to test these hypotheses; and carry out controlled intervention, defined population and demonstration-implementation studies.

Additionally, CCSP develops tracking and monitoring systems, technical field units and resources, and fosters career development and specialized education and training programs. Finally, the CCSP has initiated a multidimensional health promotion sciences program, taking advantage of technologies available from the behavioral, social, and educational sciences along with those inherent in the broad fields of information and communications.

The CCSP helps to accomplish national goals to reduce cancer incidence, morbidity, and mortality by developing strategies for identifying regions of the country with excess mortality or poor survival and then works with local/regional experts and authorities to reverse these statistics.

As the newest of the three program units, CCSP focuses its attention in an integrative, matrix fashion to support the other DCPC activities by providing staff support, perspective, and collaboration across all the phases of cancer control research.

PROGRAM OVERVIEW

CCSP activities are directed toward establishing cancer control as a scientific program. To attain this goal, the Program's branches are organized to provide resource support for the activities of the Centers and Community Oncology Program and the Prevention Program. This support is enhanced by the sponsorship of research activities, training, and technical assistance efforts. CCSP-supported activities include:

- Developing, supporting, and monitoring applied research directed toward facilitating the widespread use of proven health promotion and other cancer prevention and management techniques by health professionals, patients and their families, and the general public;
- Monitoring basic and clinical research activities to identify opportunities to develop and perfect new interventions to reduce cancer rates in populations, and to facilitate research on their application;
- Providing training opportunities for health professionals to create a national cadre of highly skilled individuals capable of identifying, researching, and applying cancer prevention and management interventions;
- Establishing program priorities, allocating resources, integrating the projects of various branches, evaluating program effectiveness, and representing the program areas in management and scientific decision-making meetings within the Institute;
- Providing programmatic and consultative support to other divisional, Institute, governmental, and private sector organizations that can facilitate the application of proven cancer control interventions in populations.

The area of maximum program thrust continues to be the development of Cancer Control Research Units (CCRU). These multi- and interdisciplinary research programs continue to provide vanguards of scientific development, testing, implementation, and evaluation for the science of cancer control. Studies across the spectrum of the phases of cancer control research are carried out in these centers of excellence, with particular attention paid to controlled intervention trials and defined populations studies.

The growth of a broad-based multidisciplinary health promotion effort continues to be a high priority. More effective ways of providing the professional and general lay public with the knowledge and means necessary to reduce cancer incidence, morbidity, and mortality continue to be a high priority.

Finally, efforts to expand the nation's armamentarium of trained health professionals, particularly experts in cancer control research and applications, have increased and are already beginning to have an effect nationally.

HIGHLIGHTS

During 1984, CCSP activities were primarily in three categories: (1) hiring new personnel to plan and develop Branch activities in accord with the overall goals of the Division; (2) planning and implementation of new Branch-directed programs; and (3) consolidation and integration with existing Divisional programs of those cancer control efforts launched in FYs 82 and 83. Over 20 new professionals and support personnel were added to the three Branches in the CCSP.

Cancer Control Applications Branch

The Cancer Control Applications Branch will continue to address the nation's needs in developing cancer control science resources as well as establishing mechanisms to track the progress of DCPC's control activities.

Special attention will be given to training new personnel for research and applications in cancer control, and identifying the needs of underserved and minority populations.

Health Promotion Sciences Branch

Particular emphasis will be placed on conceptualization of the health promotion sciences and the opportunities (based upon successes in other health-related endeavors, e.g., high blood pressure education) for application of the scientific strategies inherent in these sciences for cancer control.

A number of consensus meetings related to worksite interventions, involvement of the primary care physician, and health promotion in community settings will be held. It is anticipated that from these plannning meetings concepts for program implementation will result.

A new research program in communications systems will begin in order to increase the National Cancer Program's systematic responsiveness to the American public through the already existing Cancer Information System.

Cancer Training Branch

The Clinical Education Program (R25) for the NCI (as a whole) will be re-examined in order to increase the involvement of the broad extramural scientific community in every aspect of the NCI's goals, particularly as they relate to reducing cancer mortality substantially over the next decade and a half.

Special new incentive awards will be formulated to support the growing emphasis in the primary prevention of cancer.

PLANS

The planning efforts underway in the CCSP branches will be described in more detail under the respective branch reports which follows. A selection of those planning activities with the highest priority are summarized below.

Cancer Control Applications Branch

In FY 85, the CCAB will develop a cadre of health professionals in the U.S. versed in and committed to cancer control science. The form of this training will be through intramural mechanisms: assignment of Epidemiology Intelligence Service (EIS) officers from the Centers for Disease Control (who have chosen to carry out their two-year training affiliation with the NCI to the Division) to a preceptor in the area of interest for the EIS trainee;

the implementation of a new NIH approved training program to train cancer control scientists (Cancer Control Science Associates) over a period of three years (two years residence in DCPC, and one year placement at an institution/agency with demonstrated cancer control expertise).

Grants will be funded for defined population studies to identify cancer sites for which mortality is avoidable, to investigate cancer deaths from causes related to medical care, and to develop measures to correct precipitating factors.

Federal health agencies will be involved in the development of implementation activities in one or more of the following target areas: diet, smoking, cervical or breast cancer detection.

Health Promotion Sciences Branch

The Branch plans to develop a number of health promotion activities at the worksite and in the community; and plans to increase the involvement of primary care physicians in the process of health promotion.

Cancer Training Branch

The Branch plans to stimulate training applications in a number of scientific areas presently underserved. Particular emphasis will be given to (or continued in) prevention, epidemiology, cancer control science, including relevant behavior and social sciences, nutrition and biostatistics, and cancer nursing research at the predoctoral level.

STAFF

Acting Associate Direcotor:	Donald C. Iverson, Ph.D.
Secretarial Support:	Norine McKee

Cancer Control Applications Branch

OBJECTIVES

The primary objective of the Cancer Control Applications Branch (CCAB) is to identify opportunities for, and facilitate the application of, effective measures for preventing and controlling cancer. Major program efforts encompass building the necessary science and research bases for cancer control and ensuring that the appropriate programmatic and personnel resources will be available when needed. The program efforts include:

- Developing and administering an extramural, multidisciplinary research program on cancer control interventions through a systematic study of their effectiveness, their impact in defined populations, and their broad application for the purpose of reducing cancer incidence, morbidity, and mortality;
- Developing and maintaining a system for classifying and tracking cancer control research and programs throughout the U.S. to assess the state of the art, correlate cancer control resources with outcome measures, and estimate the needs for new research and programs;
- Participating in the development of the Division's cancer control surveillance system for monitoring progress in meeting the year 2000 goal and objectives;
- Creating an ongoing process for exchanging information and working with community organizations at all levels to set cancer control objectives and monitor progress;
- Stimulating new research and/or programs to address major cancer control problems through interactions with Federal, State, and local health agencies, cancer centers, universities, community health care practitioners, voluntary agencies, and other health-related organizations;
- Monitoring basic, clinical and applied research advances to identify new opportunities for cancer control research and programming;
- Sponsoring programs of specialized intramural and extramural educational opportunities in cancer prevention and control for DCPC staff and cancer control professionals throughout the nation (including varied opportunities designed to stimulate the development of a national cadre of highly qualified professionals capable of performing rigorous cancer prevention and control research);
- Coordinating activities, as necessary, with appropriate NCI, NIH, National Cancer Program, and other Federal and non-Federal organizations.

OVERVIEW

Established in May 1983, the CCAB was created to assist the Division in achieving the timely transfer and effective application of scientifically-derived research results to the problems and issues of cancer control in the nation. In particular, the Branch provides a focal point for DCPC efforts to work in close cooperation with community agencies and organizations for the purpose of identifying high priority cancer control issues and stimulating initiation of quality research and/or programs to address them. The objectives and ongoing programs of the Branch are also key elements in the Division's participation in the goal of obtaining a 50 percent reduction in cancer mortality rates by the year 2000. By supporting research in cancer control, classifying and monitoring resources, developing qualified personnel, and providing technical assistance for implementation in the field, the CCAB optimizes the conditions involved in achievement of the overall goal. The CCAB is organized into four functional units: Cancer Control Research, Field Programs, Career Development, and Cancer Control Resource Tracking.

The Cancer Control Research Unit aims to overcome the shortage of cancer control research in this country by supporting the development of specialized multidisciplinary research "centers of excellence" in institutions that have the expertise and resources to make progress in this area. Through grants-in-aid, it simultaneously encourages individual scientists to work in cancer control subject matter areas, and encourages institutions to develop as centers of high quality. Ultimately, this is expected to result in a flow of research applications ready to be utilized in the community at large. Cancer Control Research Unit (CCRU) grants and Cancer Control Science Program (CCSP) grants are the initial support mechanisms created for this purpose. Characteristically, CCRUs will contain large projects in specific programmatic areas such as prevention and management, and they will study defined populations from which generalizations can be made to even larger populations. CCRUs are also encouraged to establish cancer control research training programs. CCSPs are similar, but differ in that there is no requirement for defined population studies.

At present, one CCRU and three CCSPs are operational. They are multi-institutional and involve the participation of four cancer centers, three schools of public health, one health maintenance organization and a variety of hospitals, community settings and collaborating organizations. They include a total of 73 investigators (53 of these new to cancer control) working on 23 new cancer control research projects, of which 18 are prevention and five are management related. The first two defined population studies (Phase IV) in DCPC are part of the CCRU.

The CCRU at the Fred Hutchinson Cancer Research Center in Seattle, Washington, was funded in July 1983 for five years. Researchers at the Cancer Research Center collaborate with investigators from the University of Washington School of Public Health and Community Medicine. With the major research focus on prevention, the five research projects, four developmental studies, and supporting resources provide a well integrated cancer control research base for the CCRU. The approved studies are:

- Cancer Prevention with Retinol in Persons with Asbestosis (Research in Defined Populations),

- Chemoprevention of Lung Cancer with Retinol,
- Efficacy of Breast Cancer Self-Examination,
- Prevention of Cervical Cancer with Folic Acid,
- Worksite Smoking Cessation and Relapse Prevention (Research in Defined Populations),
- Smoking Cessation and Relapse Prevention: A Community Intervention Project (Developmental),
- Low Serum Selenium Levels and Subsequent Risk of Cancer (Developmental),
- Breast Self-Examination Project (Developmental),
- Primary Prevention Against Cancer Risk from Industrial Exposures to Composite Fibers (Developmental).

Three CCSPs were funded in 1983. One located at the Fox Chase Cancer Center (FCCC) in Philadelphia, received five years of support. The Illinois Cancer Council (ICC) in Chicago, and the Jonsson Comprehensive Cancer Center (JCCC), Los Angeles, each received three years funding. The studies funded under the CCSP awards include:

- Cancer Control in an Urban Neighborhood (FCCC),
- A Cancer Education Program for Older Citizens (FCCC),
- Cancer Education and Management for Patients (FCCC),
- Secondary Prevention: Comparing Traditional and Self-Directed CME (ICC),
- Compliance with Referrals for Evaluation of Possible Malignancies (ICC),
- Swallowing Rehabilitation in Cancer Patients (ICC),
- School Attendance Intervention in Pediatric Cancer Patients (ICC, Developmental),
- Physical Therapy Evaluations of Select Head and Neck Cancer Patients (ICC, Developmental),
- Smoking Cessation in Registered Nurses (JCCC),
- Compliance Behavior Among Women with Abnormal Pap Smears (JCCC),
- Outpatient Program for Comprehensive Cancer Rehabilitation (JCCC),
- The Cancer Support Group Experience (JCCC),

- Increasing Involvement in Selected Medical Care Decisions (JCCC, Developmental),

- Impact of a Breast Self-Examination Program (JCCC, Developmental).

The Field Programs Unit works with State and local agencies to encourage the planning, development, and testing of self-sustaining implementation programs that apply the latest scientific methods in cancer control. Emphasis is on providing technical assistance to increase the cancer control capability of the public health community; identification of special opportunities on the community level for reducing cancer incidence, morbidity, and mortality; and stimulating research studies in specific cancer control areas. By promoting widespread application of up-to-date cancer control technology, the program aims to build a national structure for achieving the targeted year 2000 cancer mortality goal.

The Career Development Unit aims to foster understanding of, and professional expertise in, cancer control among health professionals in the nation, and to stimulate professional interest in cancer control as a career. It offers varied educational opportunities taking place both within the NCI and externally to both NCI staff and outside health professionals. Included are colloquia, seminars, workshops, self-teaching programs, new investigator small grants, and academic and research program placement.

The Cancer Control Resource Tracking Unit develops knowledge about the composition, trends, and distribution of cancer control resources in the nation. Resources include funds, trained personnel, research results, public attitudes, and institutional and community support. The program seeks to identify where and how these elements are expended, describe their potentials and progress, compare allocations with needs, and discover program opportunities. The program correlates information on cancer control outcomes with resource information and contributes to the population science underlying estimates of future demand for cancer control resources. These functions provide a statistical and observational foundation for the work of the Division and enable it to establish factually-based policies and program priorities.

ACCOMPLISHMENTS

The year was marked by intensive in-depth planning and the beginning of implementation activity and coordination with outside organizations that have cancer control interests. Specific accomplishments are listed by program unit.

Cancer Control Research

A Request for Applications for CCRUs, embodying the new programmatic thrust, was reissued in March and mailed to more than 100 potential applicants.

The CCSP definition was modified to require the inclusion of a program theme. Henceforth, CCSPs will be treated under the standard guidelines for program project grants.

Review of the first group of CCSP applications (in response to the September 1983 RFA) was completed. Those approved will be funded in FYs 84 and 85.

Program monitoring visits made to all four current cancer control research projects showed uniformly satisfactory progress. A positive feature of the chemoprevention projects was their interaction with the general chemoprevention program of the Division.

Field Programs

A Field Programs Working Group was established to provide guidance on development of the program. Membership is composed of State and city health commissioners, epidemiologists, cancer control scientists and oncologists from large and small communities.

An RFA on Reduction in Avoidable Mortality from Cancers was issued in August. It calls for grant-supported studies to identify cancer sites for which mortality is avoidable, to investigate cancer deaths from causes related to medical care, and to develop measures to correct identified precipitating factors. The studies are to be conducted in defined populations for cancer sites to be determined by the investigators. Up to five awards are anticipated.

An RFA on Cancer Control Technical Development in Health Agencies was approved by the DCPC Board of Scientific Counselors and was issued in September. Its purpose is to stimulate improvement in the technical and scientific capabilities of public health agencies and to ascertain the extent to which these changes are reflected in improved cancer prevention and control programs. Improved capabilities are sought in oncology and public health, epidemiology and biostatistics, program planning and evaluation, and program management as they relate to cancer control. Grantees will be expected to develop implementation programs in at least one of the following target areas: diet, smoking, cervical cancer, or breast cancer detection. The projects will aim to enhance collaboration between public health agencies and existing cancer centers, and will be conducted cooperatively with division staff.

Surveys of state legislation and state health departments were conducted to determine patterns of support for, and capabilities in, cancer control. These surveys will be summarized in published reports and will be used as sources of information sharing between states and communities interested in cancer control.

Career Development

A Cancer Control Small Grants Research Program was initiated with the issuance of a RFA in March 1984. The 37 applications considered responsive to the guidelines and accepted for review proposed intervention research studies in nutrition and chemoprevention, health promotion, rehabilitation, and screening. Subject to approval on the basis of scientific merit, up to ten awards of $35,000 each will be made for studies of one or two years duration. A major objective of the program is to encourage new investigators from a variety of academic disciplines to apply their skills in scientific research to cancer control intervention research.

Epidemiology training under DCPC auspices progressed according to plan. Two officers of the Epidemiology Intelligence Service of the Centers for Disease Control in Atlanta, have completed their two years of on-site training, and will join DCPC as Senior Investigators. These two officers collaborated with a third officer in designing and implementing cancer control research dealing with diet and nutrition, and breast cancer detection.

Further, the first Public Health Service Epidemiology Training Program Fellow sponsored by DCPC, has completed the course work for the Master of Public Health degree at Johns Hopkins University and has begun a two year program of on site training in the Operations Research Branch of the Division. A second Fellow is now engaged in the required academic training. All of the program participants are M.D.s or Ph.D.s who have chosen a cancer control research career.

Planning for the Cancer Control Science Associates Program is complete. The initiation of this program has been in response to the compelling need to increase the number of scientists who are interested in, and qualified to, conduct cancer prevention and control intervention research. These scientists will ensure continued advancement of the state of the art in cancer control and improved intervention strategies for achieving the year 2000 goal. The Science Associates Program will actively recruit and train highly qualified physicians and scientists, facilitate mid-career transition to cancer control by experienced investigators, and promote their long-term participation and assimilation into the cancer control scientific research community. Up to ten Science Associates per year will be recruited when the program begins.

A cancer prevention and control curriculum is being developed, and an experienced faculty level instructor has been retained. Initially, these courses will be offered to the DCPC Cancer Control Science Associates and to DCPC professional staff. Eventually, the entire structure of this academic program will be integrated into the proposed DCPC Cancer Control Staff College.

Twenty-seven presentations on current cancer control related scientific subjects were held during the year for the division's staff and its investigators-in-training. Included were thirteen colloquia, six seminars, three program reports, and five other presentations of two or more hours each. Sixteen of these presentations were presented by the NCI staff and eleven by extramural investigators.

A Division Calendar of Outside Events has been developed and is distributed to staff on a monthly basis. The Calendar contains descriptions of national symposia, short-term educational opportunities, and other scientific activities in the fields of cancer prevention and control. In addition, curricula descriptions from the schools of public health and other academic institutions have been placed on file in the program for easy access. Other educational aids are being identified and made available on an ongoing basis.

Cancer Control Resource Tracking

The conceptual framework of the Resource Tracking Program--the Branch's newest unit--was developed during the year. As part of the planning process, a group of extramural experts in demography, epidemiology, and public health met in August with DCPC staff to advise on constructing a strong program in the demography of cancer mortality reduction. Participants also included representatives of other NIH institutes that have similar programs. Other groups will be convened to aid in the development of other resource tracking activities.

PLANS

Major CCAB plans for FY 85 include the following:

- Effort in the Research Program will concentrate on funding of CCRUs and advising on the development of CCSPs, as well as development of a better understanding of the methodology of population-based studies.
- Development of specific extramural program efforts will address the unfavorable differentials in incidence, survival, and mortality for specific cancer sites of minority ethnic populations.
- Completion of technical assistance guidelines will provide direction in management and scientific content to health agencies interested in establishing cancer control programs. Emphasis will be on setting priorities and constructing modules (including protocols) for the development of cancer control in the community in accordance with the year 2000 goal.
- Ongoing technical assistance capabilities will provide analytical and programmatic advice on the establishment of cancer control programs.
- Liaison activities will be expanded to accomplish greater interaction among agencies with cancer control interests.
- The Small Grants RFA will be re-issued. Up to 20 awards totaling $700,000 are anticipated for FY 85.
- Two more Epidemiology Intelligence Service officers will be added to work on divisional cancer prevention and control research projects.
- Up to ten participants in the Science Associates Program will be recruited.
- Curricula on the state of the art of cancer prevention and control methodology and science will be completed.

Concept proposals for the six major resource tracking components will be developed and presented for Board of Scientific Counselors approval. When implemented, these efforts will enable the cancer control program to make an accounting of the resources available for cancer control, monitor cancer control outcomes, and conduct periodic reviews of the key assumptions underlying cancer control policy. Concept subjects will be:

- Program Tracking Base: This is a research and data collection activity designed to describe and facilitate the monitoring of cancer control resources and their relationship to measures of cancer control outcomes such as mortality, length of life, and morbidity. (Studies will encompass resource measures such as trained personnel, funding, and public understanding and support, and measures of the connections between outcomes and resources such as the utilization of health services. In addition to national data, State and metropolitan area information will be included.)

- Demographic Projections for Cancer Control: This is a research activity examining implications and projections of demographic developments, such as the progressive aging of the American population, the arrival of the baby boom population of the 1950s at the age of high cancer mortality, and the reduction of other mortality risks such as cardiovascular disease.

- Measurement of Resource Outcomes: This involves conceptual and measurement efforts relating to the conditions to be changed through the application of cancer control resources. (Emphasis is on the rise of existing data resources to produce measures of outcomes supplementing the available data on cancer incidence and mortality.)

- Resource Projections: This includes estimating cancer control manpower, facilities, and activities for future years.

- Mobilization Studies: This includes research on cancer control resources focusing on the social systems to be utilized in support of cancer control.

- Science Summaries: Summaries will be developed based upon reviews of the literature of the scientific and technological state of the art in cancer control.

STAFF

Acting Chief:	Thomas J. Kean, M.P.H.
Professional Staff:	Claudia R. Baquet, M.D., M.P.H Lawrence Bergner, M.D., M.P.H. Leslie P. Boss, M.P.H., Ph.D. Carlos E. Caban, Ph.D. Jerald D. Floyd, Ed.D. (IPA) Marie C. Gardner Nancy E. Garner

Joseph W. Kelaghan, M.D.
William J. Mayer, M.D.
Lamar F. Neville, M.S.W.
Adele H. Nusbaum, M.A.
Robert O. Palmer, M.D.
Robert Parke
David C. Poskanzer, M.D., M.P.H.
Knut Ringen, Dr.P.H., M.P.H., M.H.A.

Secretarial Support:
Valerie M. Carter
Doris M. Coleman
Joyce E. Cornett
Barbara W. Redding
Cheryl J. Robertson

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Health Promotion Sciences Branch

OBJECTIVES

The Health Promotion Sciences Branch's (HPSB) mission is to support research and development programs designed to change current behaviors and/or institute new behaviors effective in reducing incidence, morbidity, or mortality from cancer.

The following are specific objectives of HPSB:

- To stimulate intervention research needed to develop, implement, and evaluate programs that offer target populations the opportunity to adopt behaviors which reduce cancer risk, facilitate early detection and appropriate cancer treatment and/or improve the quality of life of people afflicted with cancer;
- To identify and promote effective methods for the broad, systematic dissemination and application of cancer control research results;
- To provide support and collaboration with other DCPC and NCI programs which require an expertise in behavioral and social science, education, information transfer, communications, and health economics and evaluation.

OVERVIEW

The Health Promotion Sciences Branch was established in August 1983 to assist the Division to facilitate cancer control research by developing and testing interventions which are aimed at reducing cancer mortality. This Branch reflects recent health promotion and disease prevention concepts advocated by the Department of Health and Human Services.

To meet its objectives, HPSB draws on the scientific base of five major fields of study: behavioral and social sciences, education, information/communication sciences, and evaluation science. The theoretical and methodological bases of these disciplines constitute a comprehensive health promotion approach to cancer control. The Branch develops and administers an extramural applied research program to identify, implement, and evaluate health promotion interventions in cancer prevention and control. The targets of these intervention efforts are the public at large and special high-risk populations. Intervention settings for cancer control include worksites, schools, primary health care and community settings.

Health promotion research in cancer control spans the continuum from primary and secondary prevention to the treatment and management of cancer patients. Historically, the NCI's health promotion efforts have emphasized treatment and rehabilitation activities. The formation of this Branch allows for new and substantial emphasis on primary and secondary cancer prevention. The Branch will emphasize three broad research concepts: (1) the identification and promotion of the means to reduce cancer risk in individuals, organizations, and communities; (2) the identification and promotion of health-enhancing behaviors in individuals, organizations and communities; and (3) the identification and promotion of strategies to increase the acceptance of healthful life-styles in individuals, organizations, and communities. These strategies are intended to facilitate the development and diffusion of effective cancer control methods, such as smoking prevention and cessation, utilization of the Papanicolaou smear, early breast detection procedures, and dietary modifications. An increased public awareness of cancer control behaviors/technologies will be conducive to reducing premature deaths attributable to cancer.

Collaborative efforts are an integral aspect of Branch activities. HPSB staff collaborate with other Division and Institute professionals when behavioral and social science, education, information transfer, communications, health economics, and evaluation expertise are required.

A multi-award contract, the Cancer Communication Network, is a major activity sponsored by the Branch. The network is a resource for the National Cancer Program's effort to reach the public with current and factual cancer information. An additional multi-award contract was awarded to study factors which contribute to differences in cancer patient survival between black and white populations. Investigator-initiated grants also constitute a substantial proportion of the research sponsored by the Branch. Funding is currently spread across a number of program areas with special emphasis given to primary and secondary prevention, treatment, and continuing care. In the future, more emphasis will be given to primary and secondary prevention.

ACCOMPLISHMENTS

The following describes the accomplishments of HPSB during FY 84.

Branch Reorganization

A series of planning meetings was held to examine the major issues facing health promotion as an effective means of cancer control. HPSB and DCPC staff met with over 20 leading experts in health promotion and related areas. These experts were from academia, health planning agencies, and private industry. Five specific questions were addressed at these meetings: (1) What are the relevant health behaviors for cancer control? (2) Which intervention settings are most appropriate for cancer control (considering risk behaviors and types of cancer)? (3) What are the cost issues involved? (4) How should priorities be established? (5) What resources are needed to establish a coordinated health promotion research program?

The outcomes of these meetings stimulated a number of new directions for program implementation. These include an emphasis on health promotion in the worksite and in primary health care settings and schools. The target populations for this emphasis include: adults in the workplace, children, health care professionals and populations with special needs (e.g., minority ethnic groups).

Program Activities (Contracts)

Cancer Communications Network (CCN)

The CCN was established in 1976 to ensure that accurate, up-to-date information on cancer cause, prevention, early detection, diagnosis, treatment, rehabilitation, and continuing care is readily available and accessible to the public and health professionals. The CCN currently consists of 17 NCI-funded regional offices at a cost of $12 million (over the last three year funding cycle) with four additional offices participating in the network information exchange without cost to NCI. During the past year, the following significant accomplishments have taken place in the CCN program.

A publicity campaign was undertaken which advertised the nationwide toll-free line, 1-800-4 CANCER. The Cancer Information Service (CIS) number has been published in USA Today, Better Homes and Gardens, Redbook, Womens Day, and the following professional journals: Medical Times, Postgraduate Medicine, Hospitals, and The Cancer Letter. Good Morning America promoted the CIS number on two consecutive days, and "Archie" comic incorporated the telephone number into a strip aimed at giving children and young adolescents a way to inquire anonymously about smoking.

Specific audiences have been targeted to create an awareness of the CIS. For example, the CCN program, the Office of Cancer Communications (OCC), and the U.S. Surgeon General's Office collaborated on a series of media spots to educate people aged 50 and older. Dr. C. Everett Koop, the U.S. Surgeon General, was featured in promotional campaigns to make the public aware of the CIS line and the CIS fact sheet entitled "Cancer Facts For People Over 50."

The marketing techniques used to create awareness of the CIS number have also been evaluated. For example, by tagging the CIS number to a series of Public Service Announcements, which addressed the topic of cigarette smoking, CIS smoking-related inquiries rose from 590 in May 1983 to 13,523 in August 1983.

A modified form of the CCN, the Cancer Communications System (CCS), succeeded the Network in November, when its FY 84 contract expired. The Board of Scientific Counselors unanimously approved the funding of the CCS for five years. The Board also approved a concept to stimulate research which will determine the overall cancer control benefits from this service.

CIS Evaluation

A national CIS evaluation mechanism was created. The three components of this mechanism include a quality control process, a user survey, and a standardized user data set.

The use of a standardized call record form has allowed the compilation of useful data on the types of callers, the reason for calling, and the

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age, sex, race, and educational level of all callers. Analyses of these facts has indicated that CIS users are a broad cross-section of the total population.

A standardized method of staff training and a training manual have been designed to ensure a uniform high quality of training for staff members.

A standardized system of "test calls" has been implemented to monitor the quality of staff responses. Each call is judged against a set of standards. Offices are debriefed following each call, so that any pattern problems may be corrected immediately.

A standardized CIS user survey was begun in January 1984. The four cycle survey format yielded a 71 percent response rate (1,745 questionnaires). Over 93 percent of survey respondents found the CIS information useful and almost 96 percent found it clear and easy to understand. About 97 percent of callers said they would call the service again, and over 54 percent have recommended the service to others. Over 91 percent of users took some health-related action following their call. These actions included learning or practicing a self-detection technique (11.0 percent); attempting to quit or reduce smoking (12.1 percent); changing eating habits (11.6 percent); seeking more information (16.7 percent); making an appointment with a physician, clinic or hospital (22.2 percent); or sharing the information with at least one other person (54.0 percent). Over 90 percent of those who took some specific health action claimed that the CIS call was either "very important" or "somewhat important" in stimulating them to take action.

A Study of Black/White Patient Survival

The Branch and Division issued an RFP to study the differences in survival rates of black and white cancer patients using three data collection centers and one coordinating center to collect behavioral, clinical, and nutritional information and pathology status. These centers, all population-based tumor registries, have been selected and funded and are now collaborating through a contractual agreement.

Four sources of data will be used in the study: a patient interview a physician questionnaire, a slide review of pathology specimens, and a chart review of hospital records. Twenty-six hundred cancer patients (1,300 black and 1,300 white) will be recruited into the study over a two year period. Four cancer sites are of interest: breast, colon, urinary bladder, and the uterine body.

The patient interview will focus on possible racial differences in preventive health practices, help-seeking behavior for the specific cancers of interest, nutritional status prior to diagnosis, social-support systems and background characteristics predictive of survival. Interviewing is expected to begin in December 1984.

The study is designed to evaluate the relative importance of hypotheses stating that racial differences in survival may reflect differences in tumor histology, differences in host vulnerability, differences in prescribed treatments, and differences in treatment compliance. To shed light on these and other questions, the DCPC Biometry Branch will conduct a study to determine the need for targeted intervention strategies. These interventions may focus on the behavior of patients, the health care provider, and/or the interrelations between the two.

Physician Data Query (PDQ)

PDQ is an on-line computerized information base operated by the NCI. It is designed to provide physicians with up-to-date information on state-of-the-art cancer treatments, experimental protocols, and a directory of those medical associations/societies (and their individual members) that devote the majority of their time to the care of cancer patients. It is felt that PDQ can significantly reduce cancer morbidity and mortality by infusing the medical community with the most recent information on cancer treatment.

An effort to evaluate PDQ has been undertaken by two Branches within the Division, the Operations Research Branch (ORB) and HPSB. The HPSB is preparing for two PDQ sub-evaluations:

- PDQ user experience: Who is using the system? How is it being used? Are users satisfied with PDQ? How is the information generated by PDQ being applied?
- A comparison of the various versions of PDQ (as offered by commercial vendors and the National Library of Medicine) to determine the ease of access/use for each system.

Cancer Prevention Awareness

The HPSB, in collaboration with the Office of Cancer Communications, evaluated specific activities conducted during "Cancer Awareness Month." For example, an evaluation is in progress of the Saturday Evening Post article featuring NCI Director, Dr. Vincent DeVita.

Program Activities (Contract-Related)

Breast Self-Examination

A monograph addressing the state of the science of breast self-examination was published in July 1984. This monograph is a summary of a working group meeting organized by the Branch.

Cancer Risk and Nutrient Blood Levels

In collaboration with the Prevention Program, the HPSB manages a study with the Centers for Disease Control (CDC) to evaluate the relationship between cancer risk and serologic levels of specific nutrients.

The study involves 128 cancer patients and 512 matched controls from the Aspirin Myocardial Infarction Study (AMIS), which was completed in 1979. All sera samples from the AMIS study were frozen and stored at CDC.

Serologic nutrient levels (retinol, retinolbinding-protein, alpha tocopherol, beta-carotene, total carotenes, and selenium) will be compared for cases and controls at baseline and one or more annual visits. A substudy of 300 randomly stratified AMIS participants will attempt to determine relationships between nutrient levels, participants' characteristics (e.g., smoking), aspirin use, and history of the serologic samples (thawing and refreezing).

Behavioral Factors in Breast Screening Attendance

HPSB staff have been collaborating with the Cancer Detection Branch in analyzing compliance data from the Breast Cancer Detection Demonstration Project (BCDDP). The research focuses on predictors of attendance at the five annual screening examinations, and is employing a multivariate analysis with these and other related variables.

Psychological Aspects of Breast Cancer

HPSB is collaborating with the investigators from the Psychological Aspects of Breast Cancer Group, in a study of 661 Stage I or II breast cancer patients treated with mastectomy. These women were compared to 1,054 other women who underwent surgery for other organ dysfunctions, had lifethreatening illness, or acted as non-disease controls. The objective of this study is to determine the emotional impact of breast cancer and its treatment on the patient, and the patient's immediate social network. Analyses are being completed and HPSB is preparing to disseminate the results.

Program Activities (Grants)

Primary Prevention: Reseach on the Factors Leading to the Development and Prevention of Cancer

Projects in primary prevention include the following:

- Psychological and Familial Precursors of Cancer,
- Psychosocial Stress and Cancer Risk: Prospective Study,
- Behavioral Aspects in Cancer Incidence and Mortality,
- Education Outreach Methods to Hispanic Elderly,
- Project CHOICE: Cancer Prevention is Your Choice,
- Primary Prevention of Cancer in Childhood,
- Rochester Epidemiology Program Project.

Secondary Prevention: Research on the Early Detection of Cancer, Screening, and Related Behaviors

Projects in secondary prevention include the following:

- Breast Self-Examination Education: Enlisting Social Influence,
- Women's Acceptance of Breast Self-Examination,
- The Hispanic Family and Attitudes Towards Breast Cancer,
- Predictors of Breast Cancer Detection Behavior,
- Breast Cancer Detection By Breast Self-Examination.

Treatment and Management: Research on Behaviors and Other Factors Influencing Patient Satisfaction, Compliance, Side-Effects, and Disease Outcomes

Projects in treatment and management include the following:

- Physician Behavior and Cancer Patient Satisfaction,
- Behavioral Treatment for Children Receiving Cancer Therapy,
- Patient Education to Reduce Distress During Chemotherapy,
- Patient and Staff Compliance with Cancer Therapy,
- Psychosocial Collaborative Group for Cancer Control,
- Psychosocial Correlates of Survival,
- Studies in the Dissemination of Consultation Systems.

PLANS

Major plans for FY 85 include the following a reorganization of the Cancer Communication Network to establish two independent but related programs, the Cancer Communications System (CCS) and Cancer Communications System Research (CCSR).

The objectives of the CCS are:

- To develop and extend a cadre of cancer communications professionals who can plan, administer, promote and develop support materials for the cancer information and education programs which comprise the Cancer Communications System;

- To provide the general public and health professionals with accurate and current information on cancer (including additional education and information activities developed to complement and enhance the CIS system, based on community interest and need);

- To develop and maintain directories of cancer resources including agencies, organizations and services available to the general public, cancer patients and their families within a designated service area.

The goal of the CCSR is to identify, develop, implement and evaluate cancer communication research projects targeted at specific audiences, utilizing the resources of the CCS. These research projects shall include innovative ways to reach specific target groups with cancer information, and assess the impact of this knowledge on attitudes and practices. Of special interest will be studies to achieve the following:

- Stimulate network-building strategies among CCS offices and other community organizations and analyze the resulting impact;
- Compare CCS users and non-users on variables such as information seeking and/or health behavior;
- Compare differences between CIS users and non-users on variables such as delay in seeking medical care, compliance with treatment regimens, or stage of disease;
- Study the diffusion of cancer information by CCS users;
- Study the use of CCS volunteers as community opinion leaders;
- Study the link between cancer knowledge and cancer-related behavior;
- Determine the effect of follow-up reminders on the health action of CCS users.

Two projects for PDQ evaluation will be developed and funded.

- PDQ User Groups Evaluation: This project will evaluate user experience with both NLM and commercial vendor versions of PDQ. Specifically, this project will evaluate characteristics of PDQ users, how PDQ is being used, and the usefulness of the information to practicing physicians.
- PDQ Vendors Implementation Evaluation: This project will evaluate the implementation of PDQ by the system vendors, and its effect on end users and potential users. Clarity of user instruction materials, user friendliness, ease of use and access, and cost of each system are of particular interest.

Other major plans include:

- The development of initiatives soliciting Phase III and IV proposals for interventions in worksite, primary health care, school, and community settings;
- The development of a "cancer risk factor scale" and/or "cancer intervention equation" which will prioritize research in prevention and control;
- The development of research concepts to study the factors and the process in which risk-reducing/cancer preventing behaviors and actions and are adopted by populations;

- The development of research concepts to study the process of organizational change and/or policy formation which encourage risk-reducing/cancer preventing behaviors.

STAFF

Acting Chief:	Lillian R. Gigliotti, Ph.D.
Health Scientist Administrator:	Jan Howard, Ph.D.
Visiting Research Scientist:	Kelly Brownell, Ph.D. Joan Bloom, Ph.D.
Project Officer:	Judith Stein, M.A.
Health Promotion Specialist:	Edward Maibach, M.P.H.
Evaluation Consultant:	Johanna Eisenburger
Public Affairs Assistant:	Carolyn Towle
Secretarial Support:	Nadine Horne

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Cancer Training Branch

OBJECTIVES

The objectives of the Cancer Training Branch (CTB) are to:

- Plan, organize, and support a national effort to provide quality cancer research training and development for fellows and trainees ranging from predoctoral trainees to nearly-established investigators (including applied and/or basic science areas relevant to cancer cause, prevention, detection, diagnosis, treatment, control, and rehabilitation);
- Manage the Cancer Education program which encourages institutions to improve, expand, and coordinate their undergraduate, continuing education, and cancer teaching activities with emphasis on prevention, epidemiology, nutrition and control, as well as surgical and radiation oncology.

OVERVIEW

To meet the objectives of the Cancer Training Branch, the following mechanisms are employed: National Research Service Awards (including research training grants and research fellowships), Research Career Development Awards, Cancer Education Grants, Short-Term Training Awards, Preventive Oncology Academic Awards, and the newly instituted Clinical Investigator Awards. The table below shows the distribution of grants and funds in each award program for FY 1984. Following that is an overview of each award program.

Program	Number of Grants FY 84	Amount in 000s
National Research Service Awards		
Institutional	162	$20,000
Individual	185	3,280
Research Career Development	87	3,393
Research Career Awards	5	168
Preventive Oncology Academic Awards	10	734
Cancer Education Grants	77	4,977
Clinical Investigator Award	22	1,120
Veterinary Pathology Program	2	112

NRSA-Research Training Grants are institutional grants which provide universities an opportunity to develop or enhance research training at the predoctoral and/or postdoctoral level. The applicant must supply the staff and facilities for the program. The administration of the institutional training grant is handled by the program director at the institution who also selects and evaluates trainees. Students may receive up to eight years of support (five years as a predoctoral and three years as a postdoctoral) under the National Research Service Act (NRSA). The predoctoral stipend is $5,292. The level of the postdoctoral stipends depends upon the number of years of relevant postdoctoral experience and ranges from $14,040 to $19,716. Postdoctoral candidates are limited to a maximum of three years of support under NRSA. The table below shows the number of grants and trainees in the three major areas of research supported.

Area	Number of Grants	Total Trainees Pre-Doctoral	Total Trainees Post-Doctoral
Cancer Etiology and Prevention	86	388	393
Cancer Detection and Diagnosis	40	113	166
Cancer Treatment and Restorative Care	36	51	190
TOTAL	162	552	749

NRSA Research Fellowships under the Individual Postdoctoral Fellowship Program provide the opportunity for those who have attained the research doctorate or professional degree to broaden their scientific background. Applications are received in the same disciplines as the Institutional Training Grants. The postdoctoral fellow receives the same stipend level as a postdoctoral trainee. An applicant for a postdoctoral fellowship must establish his acceptance by a preceptor and must present a detailed description of the research project which he will undertake as part of his research training. The individual fellow is limited to three years of support. A senior postdoctoral fellowship is available to faculty members and others having more than seven years postdoctoral experience. The table below shows the number of fellowships awarded in each research area.

Area	Number Awarded
Cancer Etiology and Prevention	113
Cancer Detection and Diagnosis	34
Cancer Treatment and Restorative Care	38
TOTAL	185

Research Career Development Awards provide very promising young investigators the opportunity to devote full-time efforts to their development as independent investigators. Applicants must demonstrate appropriate scientific experience and achievement and must have outstanding research potential. Each candidate must be nominated by his/her sponsoring institution. The salary support is set individually with a maximum of $40,000 each year. The table below shows the number of awards in each research area.

Area	Number Awarded
Cancer Etiology and Prevention	43
Cancer Detection and Diagnosis	23
Cancer Treatment and Restorative Care	21
TOTAL	87

The Research Career Awards program provides an annual salary of $25,000 to selected cancer investigators for the duration of their research careers. Five such awards may be made by the NCI each year; however, no new awards have been granted since 1964.

Preventive Oncology Academic Awards aid in the development of preventive oncology research and curriculum design. Candidates must have a doctoral degree or equivalent and an appropriate teaching/research appointment in the sponsoring institution at the time of award. This grant mechanism presently supports up to 50 percent of the awardee's salary to a maximum of $40,000 per year and includes some salary for other personnel. Awards are made for a maximum of five years and are nonrenewable. Presently, nine grants have been awarded.

The NCI Clinical Investigator Award or Physician Investigator Development Award program, announced in March 1983, aims at developing physician-researchers in basic and applied sciences. The program was prompted by the chronic shortage of physicians-investigators, particularly surgical oncologists, radiation oncologists, preventive oncologists, psychiatrists, nutritionists and epidemiologists. The award provides up to $40,000 per year in salary plus $10,000 per year for research expenditures. Institutions apply on behalf of candidates who hold the M.D. or D.O. degrees. Candidates should have at least two, but not more than seven, years of clinical training at the postdoctoral level by the projected start date. Twenty-two awards have been granted for FY 84. These include 14 awards in internal medicine and hematology, five in surgical oncology, and three in radiology. The grants are awarded for a period of up to three years.

For present and future health professionals to have effective impact in reducing the morbidity and mortality due to cancer, they must comprehend and learn to apply the principles, methodologies, and interventions aimed at cancer control. With this purpose, the new guidelines developed for the Cancer Education Program (R25) (restated April 1984) were widely distributed.

The main objectives of the Cancer Education Program (formerly the Clinical Cancer Education Program and Professional Oncology Education Program) grants are to:

- Encourage the development and implementation of instructional activities which ensure that students and practitioners of medicine, dentistry, nursing, and public health comprehend and learn the skills needed to apply the "state-of-the-art" knowledge of cancer with particular emphasis upon its risk factors, prevention, epidemiology, control, and nutritional aspects, and the importance of surgical and radiation oncology;

- Encourage professional schools to teach such topics in an integrated multidisciplinary fashion;

- Provide undergraduate students with support for "student assistantships" to engage in short-term (up to 2 or 3 months) practical experiences in a cancer research or service activity under qualified preceptors;

- Encourage the participation of schools of public health and schools of nursing in the development of integrated cancer education programs.

In addition to schools of medicine, dentistry, public health, and specialized cancer institutions, the new guidelines extended the eligibility for Cancer Education Grants to schools of nursing that offer doctoral degrees. A prebaccalaureate research program for minority students has been incorporated within the Cancer Education Grant Program.

There are two types of Short-Term Research Training. The first type, a program for Students in Health Professional Schools (T35), was designed to ameliorate the shortage of clinical investigators by attracting highly qualified medical students into biomedical and behavioral careers. Funding for five years was provided by this program to the University of Chicago in July 1980. The award supports 26 medical students each year for three months. The second type of award is targeted for National Cancer Institute research trainees. These courses are short term, up to a week in length, and include one in epidemiology, one in histopathobiology of neoplasia, and several in various aspects of tumor biology.

The Veterinary Pathology Training Program, initiated in 1980, aims at increasing the number of board-certified veterinary pathologists and enlarging the national pool of comparative pathologists. The National Cancer Institute, in conjunction with the National Institute of Environmental Health Sciences, supports five grants in this area. Two of these are funded by the NCI. This program will expire at the end of the present project period.

ACCOMPLISHMENTS

The following list summarizes the accomplishments of the Cancer Training Branch during FY 84.

- Under the Institutional Training Grants (T32), 552 predoctorals and 749 postdoctorals (including 216 M.D.s) were supported. For the second consecutive year, the proportion of M.D. to Ph.D. research trainees was increased.

- The Individual Postdoctoral Fellowship Program supported 185 postdoctorals.

- A short-term training course was offered on the Pathobiology of Cancer in Keystone, Colorado. Ninety basic and applied research trainees and fellows, who previously lacked training in the actual disease mechanisms of cancer, actively participated.

- All FY 84 applications for the Cancer Education Grant Program responded to the new areas of emphasis--mainly cancer prevention, nutrition, and control.

- The Clinical Investigator Award was initiated to encourage more physicians to undertake careers in basic or applied research.

- Listings of available training positions for minority institutions were developed to encourage the entry of minority scientists into cancer research.

In addition, the CTB notes the following accomplishments by trainees, fellows, and awardees supported by CTB programs:

- At the University of California, San Francisco, retroviruses are being used by trainees to explore the genetic maladies that cause neoplastic growth. The product of the genes has been identified and the biochemical mechanism by which they act is being sought. The laboratory is exploring the mechanism by which retroviruses transduce oncogenes, the changes that convert proto-oncogenes to oncogenes, the role of proto-oncogenes in normal growth and development, and the possibility that proto-oncogenes are themselves, "cancer genes" within the cell.

- At Stanford, Dr. Ronald Bernenson has developed a system for selective removal of T-Cells + lymphoblasts from human bone marrow mononuclear cells using cellular immunoabsorption with monoclonal antibodies, which may be clinically useful in bone marrow transplantation.

- Dr. Katz at UCLA is developing a diagnostic assay for cancer using monoclonal antibodies. Antibody reactivity against the immunizing antigen is ascertained using an enzyme-lined immunoabsorbant assay.

- With the guidance of Dr. Frank Borber, Dr. Swerdlow at Harvard University has been working on ultrasound characterization of tissues with the scanning acoustic microprobe for staging and early detection of cancer. This computer based method for producting ultrasound images of human tissue morphology has proved able to resolve different types of tissues with about 1mm diameter separation.

- Graduate and postgraduate students at the laboratory of Dr. Lorraine J. Gudas at the Dana Farber Cancer Institute, are studying the retinoic acid induction of differentiation of mouse tumor cells and the relationship between deoxyribonucleotide metabolism and DNA mutagenesis. During cell differentiation, the tumor cells are converted from malignant, continously growing cells, to normal, growth-controlled, differentiated derivatives.

- At Harvard University, Dr. Nesrine Baturay found that the cocarcinogenic effect of concomitant exposure to radiation and benzo(a) pyrene was eliminated by treatment with a protease inhibitor.

- Dr. Gary Tarpley in Dr. Howard Temin's laboratory at the University of Wisconsin is using retroviruses as vectors for introducing oncogenes or proto-oncogenes into "normal" animal cells in culture.

- Dr. Gwendolyn Noble, working in the laboratory of Dr. Roizman at the University of Chicago, made the important discovery that antibodies of a particular specificity can block herpes virus-induced cell fusion. The results of her studies provide the first evidence that glycoprotein D of herpes simplex virus plays a role in virus-induced cell fusion.

- At Sloan Kettering Institute, Dr. Richard Cote has improved dramatically the production of human monoclonal antibody. New generated clones are rapidly growing, efficiently cloned, and are producing high levels of immunoglobulin which are stable over long periods for immunoglobulin production.

- Dr. John Arcoleo at Columbia University has developed a method for the purification of a membrane associated protein kinase C (PKC) from bovine brain and has precisely defined the optimum conditions under which this enzyme is stimulated by phorbol ester tumor promoters. The mechanism by which PKC mediates the effect of tumor promotion is being studied.

PLANS

In FY 85, the Cancer Training Branch plans the following activities:

- Make the first awards in the new NRSA Predoctoral Research Fellowship for Nurses program, conceptualized and approved during the last fiscal year;

- Restate the guidelines of the Clinical Investigator Award to improve the program by increasing its length;

- Stimulate additional training applications in prevention, epidemiology, and cancer control science, including relevant psychosocial sciences, nutrition, and biostatistics;

- Make new awards under the restated guidelines for the Cancer Education Grants;

- Stimulate the active participation of students in cancer research or service activities;

- Make the first awards relating to the recently implemented program for pre-baccalaureate minority student short-term cancer research experience;

- Restate the Preventive Oncology Academic Award guidelines to include all cancer control sciences.

Staff

Chief:	Barney C. Lepovetsky, Ph.D., J.D.
Program Directors:	Olga Joly, D.D.S., Sc.D. Janet L. Lunceford, R.N., M.S.N. Sami A. Mayyasi, Ph.D.
Technical Information Specialist:	Dorothy J. Grant
Grants Technical Assistant:	Carol Clearfield
Technical Assistant:	Elaine Carlson
Grants Clerks:	Nenomie Rush Elaine Sirkis

Appendix A

DCPC STAFF PUBLICATIONS

PUBLICATIONS

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Appendix B

INTRAMURAL PROJECT SUMMARIES (Forms PHS 6040)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00100 CPSB

PERIOD COVERED

October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

U.S.-Finland Epidemiologic Studies of Nutrition and Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Demetrius Albanes, M.D., Senior Investigator, Cancer Prevention Studies Branch, Prevention Program, DCPC, NCI (Project Officer)
Philip R. Taylor, M.D., Acting Deputy Branch Chief, CSPB, DCPC, NCI
Brenda K. Edwards, Ph.D. Biostatistician, ORB, DCPC, NCI
Anne Hartman, M.S., Health Statistician, ORB, DCPC, NCI

COOPERATING UNITS *(if any)*

National Public Health Institute, Helsinki, Finland
Operations Research Branch, DCPC

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.75	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The important relationship of diet and nutrition in the development of cancer has become well known through various research efforts. Laboratory studies have shown cancer inhibitory functions for several natural and synthetic nutrients in various models, which have been corroborated by human epidemiologic studies of nutrient intake, tissue levels and cancer incidence. Vitamin A, vitamin E, beta-carotene and selenium have been strongly implicated for their cancer preventive potential, with evidence for the former three substances warranting clinical trials of their efficacy. In addition, the roles of other nutrients in cancer cause and prevention (e.g., dietary fats and fiber) require further investigation.

The objectives of this cooperative project with the National Public Health Institute of Finland are: 1) to determine if supplementation with beta-carotene, vitamin E, or both, is effective in preventing lung cancer in smokers; 2) to assess the role of dietary selenium, vitamins A, E, and C, and fats in breast cancer development; 3) to evaluate the relationship between various levels of nutrient intake and subsequent cancer risk.

The project includes three studies. The first, a beta-carotene, vitamin E lung cancer intervention trial, is a five-year, 2x2 factorial randomized trial of daily beta-carotene (20 mg orally) or alpha tocopherol (50 mg orally) among cigarette smokers. Any reduction of lung cancer incidence in the treatment groups will be measured. The second is a breast cancer case-control study of selenium, vitamins A, E, C, fats and other nutrients, using both benign breast disease and neighborhood controls. The importance of these nutrients in breast cancer development will be assessed. Finally, the dietary survey study will assess previously collected dietary history information for a subgroup having developed cancer out of an original population cohort.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00101 CPSB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Human Studies of Diet and Nutrition

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Kathy J. Helzlsouer, M.D., Senior Investigator, CPSB, DCPC, NCI
(Principal Investigator)
Yvonne Jones, Ph.D., Staff Fellow, CPSB, DCPC, NCI
Elaine Lanza, Ph.D. Senior Investigator, DCB, DCPC, NCI
Philip R. Taylor, M.D., Acting Deputy Branch Chief, CPSB, DCPC, NCI
Blossom H. Patterson, M.A., Mathematical Statistician, ORB, DCPC, NCI

COOPERATING UNITS *(if any)*

U.S. Department of Argiculture, Beltsville Human Nutrition Research Center
Operations Research Branch, DCPC

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.5	1.4	0.1

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The role of specific dietary factors in cancer prevention has been assessed through epidemiologic studies and animal experiments. For many of these agents, information is incomplete concerning their quality and form in the food supply, bioavailability, biochemical effects and interaction with other nutrients. To further define these parameters in the human population, a cooperative research effort between the Beltsville Human Nutrition Research Center (BHNRC) and the Cancer Prevention Studies Branch, DCPC, is being conducted.

Investigations of the trace element selenium (Se) have been done during the first year. The initial phase of the Se studies examines the pharmacokinetics of a singel oral dose of selenite and selenomethionine in a healthy population. The second phase will examine the bioavailability and health effects of multiple doses of inorganic and organic selenium. A study will then be done correlating dietary intake of beta-carotene with beta-carotene levels, retinol and retinol-binding protein levels in the blood. Improved methods for analyzing carotenoids and retinoids in food and blood samples have been developed.

The effect of changing dietary fat levels and saturation of ovarian and adrenal hormones will be studied in a free-living population. This study will be explanatory to two trials of a low fat diet being conducted by the Diet and Cancer Branch. This study will also evaluate the role of dietary fat in fecal mutagen production.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00102 CPSB

PERIOD COVERED

October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Phase I Studies of Oral Synthetic Retinoids - 4-HPR

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Earl Gross, M.D., Senior Investigator, Cancer Prevention Studies Branch
Prevention Program, DCPC, NCI (Principal Investigator)

Joseph A. Tangrea, M.P.H., Pharm. Research Coordinator, CPSB, DCPC, NCI
Brenda K. Edwards, Ph.D., Biostatistician, ORB, DCPC, NCI
Philip R. Taylor, M.D., Acting Deputy Branch Chief, CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*

Dermatology Branch, NCI
Operations Research Branch, DCPC

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.9	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Phase I studies are needed to provide the parameters and characteristics of acute human toxicity, establish a maximally tolerated dose, delineate basic pharmacokinetics, and indicate a starting clinical dose for Phase III trials of the investigational drug.

Based on the in vitro and in vivo evidence that vitamin A and its synthetic analogs are active in the neoplasia process and case reports demonstrating the successful chemoprevention of basal cell carcinoma with large doses of the retinoid isotretinoin, a Phase I intramural clinical trial of a promising new oral synthetic retinoid, 4-HPR (N-4-[hydroxyphenyl]-retinamide), has been implemented. This study has the following objectives:

- Delineate acute human toxicity patterns of orally administered 4-HPR
- Determine a maximum tolerated/feasible dose (MT/FD)
- Evaluate the subacute toxicity of the MT/FD for 3 months
- Observe evidence of any therapeutic effect on specific cutaneous diseases and disorders of keratinization.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00103 CPSB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Use of Isotretinoin in Prevention of Basal Cell Carcinoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Joseph A. Tangrea, M.P.H., P.I., Pharm. Research Coordinator, CPSB, DCPC, NCI
Earl Gross, M.D., Senior Investigator, CPSB, DCPC, NCI
Philip R. Taylor, M.D., Acting Deputy Branch Chief, CPSB, DCPC, NCI
Brenda K. Edwards, Ph.D., Biostatistician, ORB, DCPC, NCI
Anne Hartman, M.S., Health Statistician, ORB, DCPC, NCI

COOPERATING UNITS *(if any)* Walter Reed Army Medical Center, Fitzsimons Army Medical Center, Brook Army Medical Center, Eisenhower Army Medical Center, Portsmouth Naval Medical Center, National Naval Medical Center, Dermatology Branch, NCI Radiology, Clinical Center, Operations Research Branch, DCPC

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.25	0.75

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The study is a 5-year, randomized, double-blind clinical trial designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinoma in a high risk population, and to examine possible side effects associated with long-term administration of low doses of isotretinoin. Approximately 1,800 evaluable subjects will be entered into the study within 12 to 18 months at 10 participating clinical centers located around the country. At each center, subjects will be randomly allocated to intervention (10 mg/day) or control (placebo) groups.

The rationale for this study includes the following. Laboratory experiments have shown that retinoids administered to animals can prevent chemical carcinogenesis. In the experimental animals, retinoids were effective even if administered after exposure to the carcinogen, and therefore the prophylactic effect of the retinoids is believed to be in the post-initiation phase, i.e., during the promotion phase of carcinogenesis. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinomas for four years in patients at higher risk of developing new tumors.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00104 CPSB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
NHANES I Epidemiologic Follow-up Survey: Chemoprevention/Nutrition Aspects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Philip R. Taylor, M.D., Acting Deputy Branch Chief, CPSB, DCPC, NCI
Gladys Block, Ph.D., Staff Fellow, ORB, DCPC, NCI

Note: This research is being developed as a collaborative effort by NCHS and various institutes at NIH.

COOPERATING UNITS *(if any)*

NCHS, NCI, NIA, NIMH, NIAAA, NHLBI, NINCDS, NIADDK, NIAID

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews
☐ (b) Human tissues
☒ (c) Neither Analysis of data originally obtained from Human Subjects/Human Tissues

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of the NHANES (National Health and Nutrition Examination Survey) Initial Epidemiologic Follow-up Survey was to conduct a longitudinal study of 14,407 adults originally surveyed in 1971-1975, to investigate subsequent health and mortality outcomes. Respondents have been traced and re-examined. Additional information was obtained from hospital records, the National Death Index and death certificates. The NHANES Initial Follow-up Survey is essentially complete.

The purpose of this intramural project is to examine the relationship of chemopreventive and nutritional factors and cancer in this representative population. This study provides an opportunity to examine these factors and potentially confounding or modifying factors in a prospective fashion, and to examine the effectiveness or toxicity of some dietary agents which are currently of great interest for cancer prevention. The relationship of baseline vitamin use, biochemical or nutritional measures and subsequent health status will be examined. In addition, descriptive data and trends in potential risk factors or protective factors over time will be examined. A continued follow-up for this cohort is expected to begin in 1985.

PHS 6040 (Rev. 1/84)

GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00105 ORB

PERIOD COVERED
October 1, 1983 - September 30. 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Research in Cancer Screening Methodology and Modeling

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Philip C. Prorok, Ph.D., Chief, SS, ORB, DCPC, NCI
(Principal Investigator)
Robert J. Connor, D.Eng., Statistician, SS, ORB, DCPC, NCI
Joan Aron, Ph.D., Staff Fellow, BB, DCE, NCI

COOPERATING UNITS *(if any)*

Biostatistics Branch, DCE

LAB/BRANCH
Operations Research Branch, DCPC

SECTION
Screening Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.65	0.60	0.05

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews
☐ (b) Human tissues
☒ (c) Neither Analysis of data originally obtained from Human Subjects/Human Tissues

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The focus of this project is development and refinement of statistical procedures for the design and analysis of screening, detection, and related studies in cancer. Statistical problems under investigation include sample size determination, comparison of analysis methods, and development of stopping rules for screening trials. Each of these problem areas is common to screening and prevention trials in which the Division participates, but the methods for screening studies must address the special lead time and length biases inherent in screening programs.

The research includes investigation of techniques to estimate and adjust for screening biases in the analysis of survival data, and the study of the relationship between long-term mortality and short-term outcome measures, such as stage shift. Probabilistic models of disease and screening are being developed to aid in the interpretation and evaluation of data from screening programs. A breast cancer screening model relating doubling time to survival is under derivation in collaboration with the Biostatistics Branch, DCE. Characteristics of case-control studies in the context of screening evaluation are also being considered.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00106 ORB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies in Cancer Screening

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Philip C. Prorok, Ph.D., Chief, SS, ORB, DCPC, NCI
(Principal Investigator)
Robert J. Connor, D.Eng., Statistician, SS, ORB, DCPC, NCI
Joan Aron, Ph.D., Staff Fellow, BB, DCE, NCI
Thomas Mason, Ph.D., Epidemiologist, Population Studies Section, DCE, NCI

COOPERATING UNITS *(if any)*
Division of Cancer Etiology, NCI
National Institute for Occupational Safety and Health

LAB/BRANCH
Operations Research Branch, DCPC

SECTION
Screening Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.65	0.60	0.05

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Data from several cancer screening studies are being analyzed to gain a better understanding of the impact and consequences of such screening in various population settings, and to develop new techniques for data analysis. Results from the Health Insurance Plan of New York breast cancer screening trial continue to indicate a long-term reduction in breast cancer mortality. In collaboration with the Biostatistics Branch, DCE, patterns of case survival and cause of death are being related to population mortality measures to further assess the nature of the screening benefit.

A group collaborating through the International Agency for Research on Cancer is analyzing the cervical cancer screening programs in Scandinavia and Aberdeen, Scotland to estimate false negative rates and natural history characteristics, and relate these to the varying screening parameters in the participating countries. Two occupational high risk groups are under scrutiny. In collaboration with DCE, the bladder cancer screening program at the DuPont Company is being analyzed to relate disease characteristics and outcome to cytology and blood tests, smoking history and chemical exposure. With DCE and the National Institute of Occupational Safety and Health, updated follow-up data are being collected in a study of sputum cytology screening for lung cancer among uranium miners. The relationships among cytology classification, radiation exposure, smoking history, lung cancer, and mortality data will be analyzed. Participation in an International Union Against Cancer screening evaluation project resulted in a monograph on methodologic issues in screening, plus evaluation of lung, bladder and oral cancer screening.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00107 ORB

PERIOD COVERED

October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Design and Analysis of Pharmacokinetic Studies of Selenium

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Blossom H. Patterson, M.A., Mathematical Statistician, ORB, DCPC, NCI
(Principal Investigator)
Loren A. Zech, M.D., Senior Scientist, LTB, DCBC, NCI
(On leave from OD, NHLBI).

COOPERATING UNITS *(if any)*

Cancer Prevention Studies Branch
Laboratory of Mathematical Biology, DCPC

LAB/BRANCH

Operations Research Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.25	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews
☐ (b) Human tissues
☒ (c) Neither

Analysis of data originally obtained from Human Subjects/Human Tissues

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Selenium is a possible cancer prevention agent, and is being considered for use in intervention trials. Two studies in collaboration with the Cancer Prevention Studies Branch, DCPC (Z01 CN 00101 CPSB) are in progress which will provide information on the bioavailability and pharmacokinetics of selenium in its prototype forms - sodium selenite (inorganic form) and selenomethionine (organic form). This information is unavailable for these agents in the dose currently considered optimal, and is necessary to the determination of time and manner of administration. The initial study is the Selenium Pharmacokinetic Study. Parameters such as percent absorption, maximum concentration, time to maximum concentration, and half-life are estimated for a single dose and compared in both fasting and nonfasting subjects. A second study, the Selenium Chronic Supplementation Study, examines and compares the effects of multiple dosing on the absorption, distribution, and excretion of these two forms of selenium and a placebo. The Operations Research Branch, in cooperation with the Cancer Prevention Studies Branch, will function as a data collection center and has primary responsibility for the study design and data analysis.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00108 ORB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of Cancer Control Epidemiology and Tracking

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Douglas L. Weed, M.D., Ph.D., Senior Staff Fellow, ORB, DCPC, NCI
(Principal Investigator)

COOPERATING UNITS *(if any)*

Biometry Branch, DCPC

LAB/BRANCH
Operations Research Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	1.0	.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to develop the methodology of cancer control epidemiology, with emphasis on its analytic models, its data tracking needs, and its foundations in biological and statistical theory. Research areas include: concepts of cause and prevention; logic and methods of inference; alternative models to cause and chance; the scientific, engineering, technological and ethical implications of cancer control research; the relationship of carcinogenesis models to models of interaction; problems of self-selection and selection bias; using absolute and relative measures to assess the effects of cancer control interventions; and an evaluation of the data-tracking needs of large defined populations suitable for cancer control intervention studies.

PHS 6040 (Rev. 1/84)

GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00109 ORB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Data Management and Design of Clinical Trials for Cancer Prevention and Control

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Brenda K. Edwards, Ph.D., Biostatistician, ORB, DCPC, NCI
(Principal Investigator)
Anne Hartman, M.S., Statistician, ORB, DCPC, NCI
Blossom H. Patterson, M.A., Mathematical Statistician, ORB, DCPC, NCI
Oscar M. Chavez, Statistical Assistant, ORB, DCPC, NCI

COOPERATING UNITS *(if any)*

Cancer Prevention Studies Branch, DCPC

LAB/BRANCH
Operations Research Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.75	0.25

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews
☐ (b) Human tissues
☒ (c) Neither Analysis of data originally obtained from Human Subjects/Human Tissues

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several activities important for the design, data management, and implementation of the intramural controlled trials (Z01 CN 00103 CPSB and Z01 CN 00100 CPSB) have been undertaken during this fiscal year. In addition, broader research in controlled clinical trials has been conducted. Descriptions follow.

In a cancer prevention trial, the observed treatment effect may be diluted by the presence of preexisting cases; sample size must be increased to compensate for this effect. Prescreening may reduce the number of such cases. Appropriate methods of sample size estimation and a cost model are being developed.

A study to estimate the incidence of new basal cell carcinoma (BCC) in individuals already exhibiting previous BCCs was undertaken. Results from this study provide confirmatory evidence to support an estimate of the incidence of new BCCs used to plan sample size requirements for a chemoprevention trial with BCC patients (Z01 CN 00103 CPSB).

The Operations research Branch is acting as the Data Coordinating Center for the "Use of Isotretinoin in the Prevention of Basal Cell Carcinoma" chemoprevention trial (Z01 CN 00103 CPSB). Responsibilities include all of the usual ones for a data coordinating center as well as preparation and administration of a training program for both the clinical study coordinators and the principal investigators, and collaboration in the interim and final analyses of study data.

Pilot studies are a major component of large intervention trials, since the feasibility of many parameters needs to be tested before launching into a study with 2,000 or 20,000 patients. The "Use of Isotretinoin in the Prevention of Basal Cell Carcinoma" pilot study, completed in FY 1984 in collaboration with the *Prevention Program, demonstrates* some of these parameters.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00110 ORB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Methodologic Studies of Dietary Assessment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gladys Block, Ph.D., Staff Fellow, ORB, DCPC, NCI (Principal Investigator)
Anne Hartman, M.S., Health Statistician, ORB, DCPC, NCI
Janet Sobell, M.S., Epidemiologist, ORB, DCPC, NCI

COOPERATING UNITS *(if any)*

Cancer Prevention Studies Branch, DCPC; National Center for Health Statistics; National Institute on Aging

LAB/BRANCH
Operations Research Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	1.0	0.1

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A number of projects are in progress to evaluate and improve the reliability and validity of dietary assessment. A self-administered diet history questionnaire has been developed and piloted, and evaluations of the food list and quantitation methods indicate a high degree of agreement with a reference method. Field validation studies are under way in several different populations and using several different reference methods.

Efforts toward the improvement of nutrient estimation in quantified diet questionnaires have included the development of a nutrient dietant and portion sizes using a data-based approach, based on data from 12,000 respondents in the National Health and Nutrition Examination Survey. A data management and diet analysis system for use with the self-administered diet history has also been developed.

In conjunction with the U.S.-Finland Beta-Carotene, Alpha-Tocopherol Lung Cancer Prevention Trial, studies have been designed to assess the validity and reliability of the extensive, self-administered instruments used in that trial.

An evaluation of the accuracy of retrospective dietary assessment is being carried out, using subjects who provided multiple seven-day diet diaries seven to fifteen years ago. Their ability to provide information about their diet during that time period will be evaluated using both an interview and a self-administered questionnaire. In addition to the above dietary assessment methodology studies, an effort has been undertaken to evaluate the impact of improved carotenoid analysis on estimated risk levels in epidemiologic studies.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00111 ORB

PERIOD COVERED

October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Consumption of Foods and Supplements Potentially Related to Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gladys Block, Ph.D., Staff Fellow, ORB, DCPC, NCI (Principal Investigator)
Blossom H. Patterson, M.A., Mathematical Statistician, ORB, DCPC, NCI
Anne Hartman, M.S., Health Statistician, ORB, DCPC, NCI
Philip R. Taylor, M.D., Acting Deputy Branch Chief, CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*

Cancer Prevention Studies Branch, DCPC
National Center for Health Statistics

LAB/BRANCH

Operations Research Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	1.0	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several projects are ongoing, designed to identify indicator foods for methodologic uses, and to describe the population's behavior with respect to potentially protective or harmful foods or nutritional supplements. Such efforts support the dietary assessments and monitoring necessary for cancer control, provide data on which to base population interventions or strategies, and shed light on factors which may influence observed subgroup differences in cancer incidence or survival.

Quantitative data on nutrient sources in the U.S. diet for each of 18 nutrients have been developed. These data permit the identification of foods which make quantitatively important contributions to the population's intake of, for example, vitamin A or saturated fat. A follow-on project will provide this type of analysis for demographic or geographic subgroups. This information may aid in efforts to improve dietary assessment and dietary behavior in subgroups, as well as to understand possible reasons for observed differences in cancer incidence or survival.

An analysis of the proportion of Americans consuming potentially beneficial or harmful foods, such as high-fiber foods or red meat, will be carried out for each of several categories by race, sex, age and poverty status. The results may be useful in dietary interventions and public information campaigns. Demographic and behavioral correlates of vitamin supplement usage will be described using a large representative national sample.

PHS 6040 (Rev. 1/84)

GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00112 CPSB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Nutrition Intervention Study in Esophageal Cancer in Linxian, China

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Philip R. Taylor, M.D., Acting Deputy Branch Chief, CPSB, DCPC, NCI
(Project Officer)

Joseph A. Tangrea, M.P.H., Pharm. Research Coordinator, CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*

Cancer Institute, Chinese Academy of Medical Sciences, Beijing, The People's Republic of China
Division of Cancer Etiology, NCI

LAB/BRANCH

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	.75	.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to conduct two intervention trials using multiple vitamin-mineral supplements to evaluate the relationship between such supplements and esophageal cancer incidence and mortality. One trial will be conducted in patients diagnosed with esophageal dysplasia (n = 2400) and the other in the general population in a high risk region (n = 28,000). The effect of these supplements on regression/progression of esophageal dysplasia and total cancer incidence, total cancer mortality, and total mortality will be evaluated. These two studies will be conducted in Linxian (Hena Province) in the People's Republic of China (PRC). Linxian, a rural country with population 800,000, was selected because it has the highest rate of esophageal cancer in the world (>100/100,000) and because there is suspicion that the population's chronic deficiencies of multiple nutrients may be etiologically involved.

This study is being conducted jointly by the Environmental Epidemiology Branch of the Division of Cancer Etiology and the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control at the NCI in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences.

PHS 6040 (Rev. 1/84)

GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00113 BB

PERIOD COVERED

October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cancer in Oriental Populations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Haitung King, Ph.D., Research Sociologist, BB, DCPC, NCI (Principal Investigator)
Frances B. Locke, M.S., Statistician, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Biometric Research and Analytic Studies Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	2.0	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies of cancer among Chinese and Japanese in the U.S. and homeland counterparts are conducted to ascertain the transitional effect at geographical and generational (nativity) levels, and to elicit clues to the mapping out of cancer prevention and control programs for U.S. Orientals and other populations. The past limitation on U.S. Chinese studies was resolved by the release of the 1975 People's Republic of China (PRC) national mortality survey findings. Studies include:

- A study of cancer mortality among the Chinese in the U.S. (by nativity), Hong Kong, and Guangdong Province in the PRC was undertaken to examine migration effects because the majority of U.S. and Hong Kong Chinese originated in Guangdong.
- A second project, based on a similar hypothesis of the first study was initiated comparing cancer mortality in Taiwan province and Singapore with that for Fujien province.
- A third study analyzes the incidence, mortality, and survival statistics on Chinese and Japanese groups in the SEER areas of San Francisco and Hawaii with a comparison of incidence in Los Angeles. Emphasis is placed on inter-community differences, on which future community specific cancer control and prevention programs may be based.

Future plans include extending the 1960 U.S. data and comparable statistics on Asian Chinese for a two decade trend analysis; acquiring local dialect data in Fujien, for comparison with the sub-population groups in Singapore; initiating field studies on life style changes in relation to cancer control and prevention.

PHS 6040 (Rev. 1/84)

GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CN 00114 BB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Morbidity Among Long-Term Survivors of Childhood Cancer and Their Offspring

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
Max H. Myers, Ph.D., Chief, BRASS, BB, DCPC, NCI (Principal Investigator)
John J. Mulvihill, M.D., Chief, CGS, CEB, DCE, NCI
Roger R. Connelly, M.S., Statistician, BRASS, BB, DCPC, NCI
Sandra Abbott, M.S., Statistician, BRASS, BB, DCPC, NCI
M. Darlene Naughton, Computer Systems Analyst, BRASS, BB, DCPC, NCI

COOPERATING UNITS (if any)
University of Iowa; University of Kansas; University of Texas System Cancer Center; Yale University School of Medicine; California State Department of Health; ORI, Inc.

LAB/BRANCH
Biometry Branch, DCPC and Clinical Epidemiology Branch, DCE

SECTION
Biometric Research and Analytic Studies Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	1.1	

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This study, done in collaboration with investigators in the Division of Cancer Etiology, was designed to detect the effects of cancer and its treatment on childhood patients who survived to adulthood as well to detect any effects that might have been transmitted to offspring. Specific issues for investigation were the occurrence of subsequent primary cancers, quality of life, late morbidity other than cancer, infertility among the cases, and cancer and birth defects among offspring. Cases were selected from 5 U.S. cancer registries that had a histologically confirmed malignant neoplasm or brain tumor diagnosed under age 20 years, between 1945 and 1974, who survived at least 5 years after diagnosis, and who reached the age of 21 years. Up to 2 sibling controls were selected for each case with sequential priority given to full blood relationship, same sex, closest in age. Interviewer administered questionnaires were obtained for 2,305 (91%) of the cases and 3,299 (77%) of the controls.

Preliminary observations indicate that cancer occurred in 0.34% of offspring of cases, versus 0.21% of offspring of controls. These two rates were not significantly different from each other or from general population expectations. One or more major birth defects occurred in 8.3% of case children and 7.4% of control children; these results were not significantly different.

The quality of life issues investigated in this study included graduation from high school, age at graduation, marital status, parental status, and health interference with taking a job or holding a job. The percentages who graduated from high school were similar for cases and controls as were the ages at graduation. When compared with controls, higher percentages of cases reported they never married, didn't marry because of a health problem, married but had no children, and had health problems that interfered with vocational status.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00115 BB

PERIOD COVERED

October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Descriptive Cancer Epidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Max H. Myers, Ph.D., Chief, BRASS, BB, DCPC, NCI (Principal Investigator)
Benjamin F. Hankey, Sc.D., Statistician, BRASS, BB, DCPC, NCI
Roger R. Connelly, M.S., Statistician, BRASS, BB, DCPC, NCI
Anne Baranovsky, M.S., Statistician, BRASS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biometry Branch, DCPC

SECTION

Biometric Research and Analytic Studies Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.3	4.6	2.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews
☐ (b) Human tissues
☒ (c) Neither Analysis of data originally obtained from Human Subjects/Human Tissue

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The primary purpose of this project is to describe and evaluate the distribution of cancer in the United States in terms of age, sex, race, place and time in order to identify subgroups that offer possibilities for mortality reduction through intervention. Biostatistical techniques are applied to cancer morbidity and mortality rates to determine whether observed variations within and between subgroups of the population are more than fortuitous. A recent study of colorectal cancer showed that white residents of 45 countries exhibited statistically significant excess mortality rates for this disease. Incidence rates for the three countries that were within the SEER Program were significantly elevated while extent of disease and survival characteristics were only trivially different from other patients in the SEER Program. Thus, if these results hold for residents of counties not in the SEER Program, mortality reduction intervention for colorectal cancer should be based on prevention.

In another study, no substantial temporal increases in pancreatic cancer incidence rates were observed during 1973-81. International comparisons of pancreatic cancer incidence rates may be biased, since autopsy rates vary appreciably between countries, and international correlations suggesting a more important role for coffee consumption than for cigarette smoking in the etiology of pancreatic cancer may not be entirely valid. A multiple primary cancer study of women with at least two nonsimultaneous breast cancers, and with the second breast cancer occuring in the contralateral breast, provided information on the association between the stage of disease for the first two primary cancers. A statistically significant, positive association was found which is consistent with an immunological hypothesis regarding the effect of cell mediated immunity associated with first breast cancer or second breast cancer behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00116 BB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Statistical Methodology Research

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David P. Byar, Chief, CDTS, BB, DCPC, NCI
(Principal Investigator)
Mitchell H. Gail, M.D., Ph.D., Statistician, CDTS, BB, DCPC, NCI
David L. Levin, M.D., Senior Investigator, CDTS, BB, DCPC, NCI
Steven Piantadosi, M.D., Ph.D., Medical Staff Fellow, CDTS, BB, DCPC, NCI
Donald K. Corle, M.S., Computer Systems Analyst, CDTS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.11	2.6	.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to conduct research in statistical methods and computer techniques with particular emphasis on those appropriate for analyzing data from clinical and diagnostic trials and epidemiological studies of cancer. Many of the problems studied under this project arise from the consultative activities of the Section.

During the past year the use of factorial designs for clinical trials of agents which might prevent the development of cancer has been studied, with particular attention paid to nonlinear end points and the effect of plausible interactions on statistical power. Another major project involved a systematic analysis of data on stage at diagnosis and survival for patients with breast or colon cancer in all SEER counties in an effort to determine whether some areas had unusually poor survival or high stage at diagnosis. Another important area of methodologic research was the analysis of maps of cancer mortality by state economic areas (SEA) for the entire country. Using lung cancer in white males as an example, regression methods were used to relate geographic, economic, and demographic data to the observed mortality patterns, paying special attention to the problem of spatial autocorrelation.

Other methodologic problems studied included the assessment of apparent treatment-covariate interactions arising in the analysis of data from clinical trials, sample size calculations for case-control studies with quantitative exposures, the effect on the size of tests for trend of optimal grouping of adjacent categories, and the use of case-control data for designing intervention studies for high risk groups.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00117 BB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies of Cancer Patient Survival

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Benjamin F. Hankey, Sc.D., Statistician, BRASS, BB, DCPC, NCI
(Principal Investigator)
Max H. Myers, Ph.D., Chief, BRASS, BB, DCPC, NCI
Sandra Abbott, M.S., Statistician, BRASS, BB, DCPC, NCI
Herman Heise, Statistician, BRASS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

Health Promotion Sciences Branch, DCPC
Breast Cancer Cooperative Group

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Biometry Research and Analytic Studies Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.8	1.5	0.3

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A study of black/white differences in cancer patient survival for cancers of the female breast, colon, urinary bladder, and uterine corpus has been initiated in collaboration with the Health Promotion Science Branch, DCPC. Data will be collected on 2,600 patients with information to be obtained on behavioral and nutritional factors, extent of disease, pathological characteristics of the primary tumor, and treatment.

Currently in progress are studies comparing the survival of patients treated at comprehensive cancer centers with patients from geographic areas covered by the SEER Program. Preliminary findings suggest that improvement in the management of Hodgkin's disease is possible in the general medical community through the application of existing knowledge. Other sites will be studied in this regard.

Trends in survival for childhood cancers have been studied for patients diagnosed during the 1970s. Survival has improved for all forms of childhood cancers with substantial improvements found for acute lymphocytic leukemia and soft tissue sarcoma. Recurrence in patients with soft tissue sarcoma has been studied and found to be associated with extension and location of the primary tumor as well as its histologic grade.

Clinical trial data testing the additive effect of vincristine (because of its known central nervous system toxicity and high cost) to cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone in the treatment of advanced breast cancer were analyzed. Vincristine was not found to be an important part of the treatment regimen and patients receiving vincristine did experience significantly more central nervous system toxicity.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00118 BB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Surveillance, Epidemiology, and End Results (SEER) Program

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

John L. Young, Jr., Dr.P.H., Chief, DAS, BB, DCPC, NCI (Principal Investigator)
Earl S. Pollack, Sc.D., Chief, BB, DCPC, NCI
A. J. Asire, M.S., Statistician, DAS, BB, NCI
B. J. Cicero, Medical Record Librarian, DAS, BB, NCI
J. B. Cunningham, Medical Record Librarian, DAS, BB, NCI
M. M. Cusano, Computer Systems Analyst, DAS, BB, NCI
J. W. Horm, M.S., Statistician, DAS, BB, NCI
M. A. Kruse, Medical Record Librarian, DAS, BB, NCI
W. I. Louri , Jr., M.P.H., Statistician, DAS, BB, NCI
C. L. Percy, M.S.P.H., Statistician, DAS, BB, NCI
L. A. Ries, M.S., Statistician, DAS, BB, NCI
E. M. Shambaugh, M.A., Statistician, DAS, BB, NCI
V. D. Van Holten, Computer Specialist, DAS, BB, NCI

COOPERATING UNITS *(if any)* U. of CA, San Francisco; CT Dept. of Health; Fred Hutchinson Cancer Res. Ctr., Seattle; Res. Corp. of the U. of HI; U. of IA; MI Cancer Found.; N. CA Cancer Pgm; NJ Dept. of Health; Emory U.: ORI, Inc.; C'wealth of Puerto Rico Dept. of Health, Yale U.

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Demographic Analysis Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
15	12	3

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Data on cancer patients diagnosed from year of entry into the SEER Program through 1982 were submitted to the NCI by the 10 participants in December 1983. One new registry, the State of New Jersey, was added to increase the coverage of black and Hispanic populations, but no data have been received from this registry as of yet, although once included, coverage will be retrospective to January 1, 1979. The 10 participants submitting data also supplied follow-up data through December 31, 1982 for all patients diagnosed 1973-81.

Survival rates have been examined for eight racial/ethnic groups in the United States. For many primary sites, Japanese experienced the highest survival rates and American Indians the lowest. In comparison to Anglos, Japanese had higher survival for cancers of the stomach, colon, prostate, and breast. The higher survival from stomach and breast cancers persisted even when controlling for age of patient and stage of disease at diagnosis. Survival rates for blacks were much lower than those for whites for cancers of the corpus uteri and urinary bladder. Survival rates for Chinese and Hawaiians were roughly comparable to those for Anglos, while survival rates for Filipinos tended to be similar to those for blacks. Incidence rates for individual years 1973-81 and for the composite of 1973-77 and 1978-81 are being published for each SEER area and each ethnic group represented in the Program. Mortality data for these same time periods have been obtained from the National Center for Health Statistics and are also being published. For 1981, the age-adjusted incidence for all cancer sites combined, both sexes combined was 342.2 per 100,000 population while the age-adjusted mortality was 167.1 per 100,000.

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